SYNTHETIC STUDIES OF DETOXIN COMPLEX II: SYNTHESES OF DETOXIN B1 AND B3

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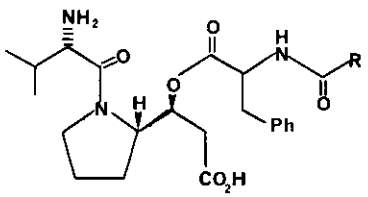
Abstract - Syntheses of title compounds from L-proline are described.

The detoxin complex constitutes an interesting group of depsipeptides.[1] This complex, made up of metabolites produced by Streptomyces caespitosus var detoxicus 7072 GC_1, is of great interest for its detoxification effect against the antibiotic blasticidin S both in animal and plant cells. We are pursuing a broad program dealing with the total synthesis of detoxinine [2], the main constituent of the complex, as well as the syntheses of other members of the detoxin complex. As a continuation of our investigations in this area, we wish to report here the syntheses of detoxin B1 (1) and B3 (2) (Figure 1), the only two congeners of the complex that contain 5-deoxydetoxinine[1f,g] in place of detoxinine.



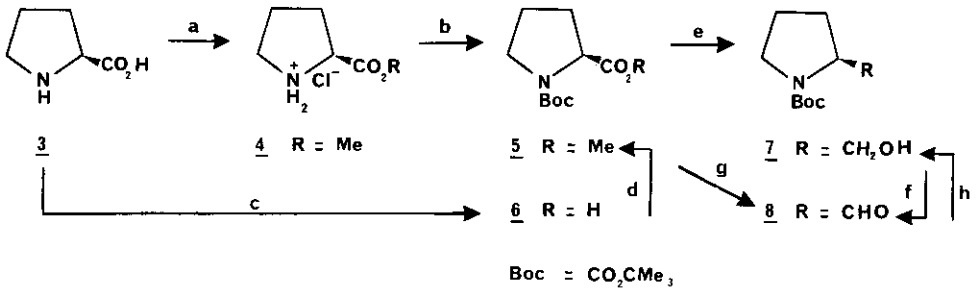
Detoxin B1 1 **R = Me**

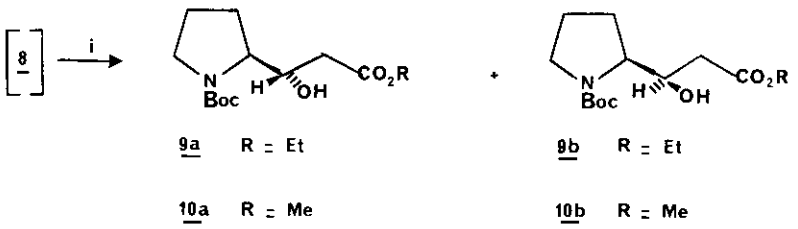
Detoxin B3 2 **R = *i*-Pr**

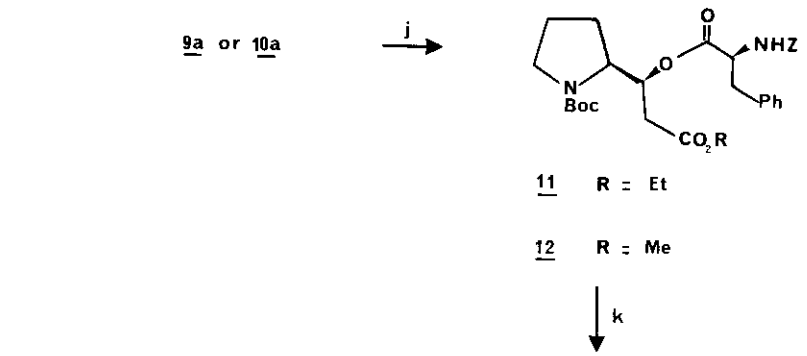
Figure 1

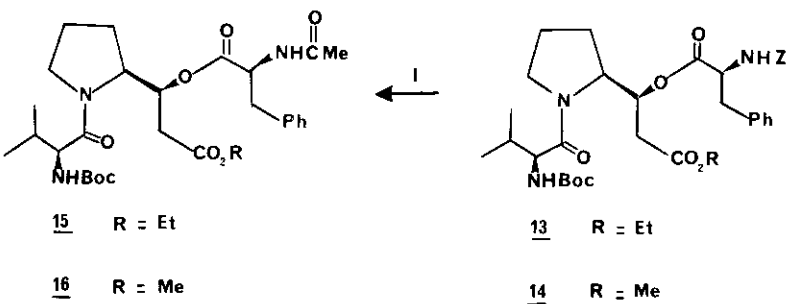
Our synthesis (Scheme 1) begins with commercially available L-proline (3) which was first converted to methyl N-(tert-butyloxycarbonyl)-L-prolinate (5)[3] by two different routes. L-Proline was esterified[4] with methanol via the acid chloride to give the corresponding methyl ester as the hydrochloride 4 in quantitative yield. Neutralization of 4 in situ, followed by treatment of the resulting amine with di-tert-butyl dicarbonate, afforded 5 in 96% yield, after purification by flash chromatography. A somewhat less satisfactory route to 5 was the introduction of the

Scheme 1









[a] $SOCl_2$, MeOH; [b] $(Boc)_2O$, NEt_3, CH_2Cl_2; [c] $(Boc)_2O$, 1N NaOH, dioxane-water; [d] MeOH, CH_2Cl_2, DCC, DMAP; [e] $NaBH_4$, LiCl, EtOH, THF; [f] SO_3·Py, DMSO, NEt_3 or $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2, -78°C→RT; [g] DIBAL, toluene, -78°C, 6 min; [h] $NaBH_4$, EtOH; [i] Zn-Cu, $BrCH_2CO_2R$ (R=Me, Et), ether, 45°C; [j] Z-Phe-OH, DCC, DMAP, CH_2Cl_2; [k] 1. TFA, CH_2Cl_2; 2. NEt_3, Boc-Val-OH, DCC, HOBT, CH_2Cl_2; [l] 1. H_2, Pd/C, EtOH; 2. MeCOCl, Py, CH_2Cl_2.

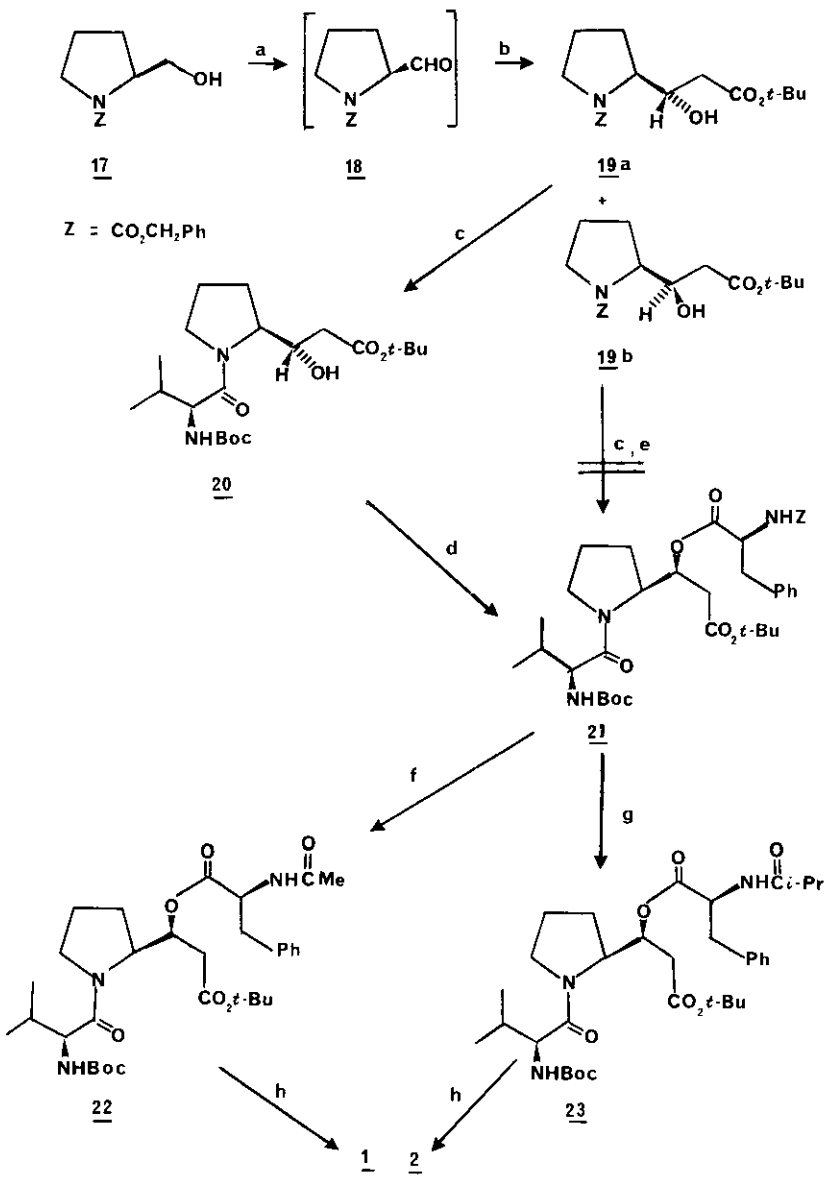
tert-butyloxycarbonyl (Boc) group first, followed by conversion of the resulting Boc-proline (6) to 5 under carbodiimide mediated esterification conditions.[5] This sequence afforded 5 in 73% yield from 3. Ester 5 was conveniently reduced to N-tert-butyloxycarbonyl L-prolinol (7)[6] in 92% yield using lithium chloride-sodium borohydride in an ethanol:tetrahydrofuran solvent mixture.[7] Subsequent oxidation of alcohol 7 to aldehyde 8 was effected either using sulfur trioxide-pyridine and dimethylsulfoxide in the presence of triethylamine[8] or oxalyl chloride and activated dimethylsulfoxide.[9] This reduction-oxidation sequence was found to be superior to the direct reduction[10] of ester 5 to aldehyde 8 with DIBAL in toluene, as in the later case the product was contaminated with alcohol to the extent of 5-8% as determined by ^{1}H nmr. To establish the optical integrity of the aldehyde obtained via oxidation, a sample was reduced with sodium borohydride and the optical rotation of the resulting alcohol was compared with the known value for this compound. The results indicated the aldehyde to be 99% optically pure.

Reaction of aldehyde 8 with ethyl or methyl bromoacetate and a zinc-copper couple under Reformatsky conditions[11] produced the hydroxy esters 9a, 10a, and 9b, 10b as a 1:1 mixture of chromatographically separable diastereomers in 85% yield for the two steps. The optical purity of the hydroxy esters was established by Mosher's ester method.[12] Conversion of either 9a or 9b to α-methoxy-α-trifluoromethylphenyl acetic (MTPA) ester and analysis of ^{1}H and ^{19}F chemical shifts (peak area integration) indicated the diastereomers to be > 99% optically pure.

Depsipeptides 11 and 12 were prepared in 86% yield from 9a and 10a by esterification of N-benzyloxycarbonyl-L-phenylalanine via reaction with N,N'-dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP)[5] in methylene chloride. Compounds 11 and 12 were treated with trifluoroacetic acid (TFA) to remove the tert-butyloxycarbonyl group at the proline amino function. Neutralization in situ of the resulting trifluoroacetate salt and condensation with Boc-L-valine as mediated by DCC and 1-hydroxybenzotriazole (HOBT)[13] gave tridepsipeptides 13 and 14 in 90% yield. Catalytic hydrogenation effected the removal of the benzyloxycarbonyl (Z) group to afford the free amine which on acylation with acetyl chloride yielded 15 and 16 in 80% yield. However, all attempts to remove the ester functionality from these compounds were unsuccessful. This therefore led us to revise our synthetic strategy.

N-Benzyloxycarbonyl-L-prolinol (17)[14] (Scheme 2) was oxidized to the corresponding aldehyde 18 using Swern conditions.[9] Reaction of aldehyde 18 with tert-butyl bromoacetate and zinc-copper couple gave the hydroxy esters 19a and 19b as a 1.5:1 mixture of diastereomers in 80% yield for the two steps. A single crystal X-ray analysis of 19b served as the basis for the structural assignment. An ORTEP diagram of 19b is shown in Figure 2. The benzyloxycarbonyl group in the S,S diastereomer (19a) was then removed by catalytic hydrogenation. Condensation of the

Scheme 2



[a] $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2; [b] Zn-Cu, $BrCH_2CO_2$t-Bu, ether; [c] 1. H_2, Pd/C, EtOH; 2. Boc-Val-OH, DCC, HOBT, CH_2Cl_2; [d] Z-Phe-OH, DCC, DMAP, CH_2Cl_2; [e] Z-Phe-OH, TPP, DEAD, THF; [f] 1. H_2, Pd/C, EtOH; 2. MeCOCl, DMAP, CH_2Cl_2; [g] 1. H_2, Pd/C, EtOH; 2. i-$PrCO_2H$, DCC, HOBT, CH_2Cl_2; [h] TMSCl, NaI, MeCN.

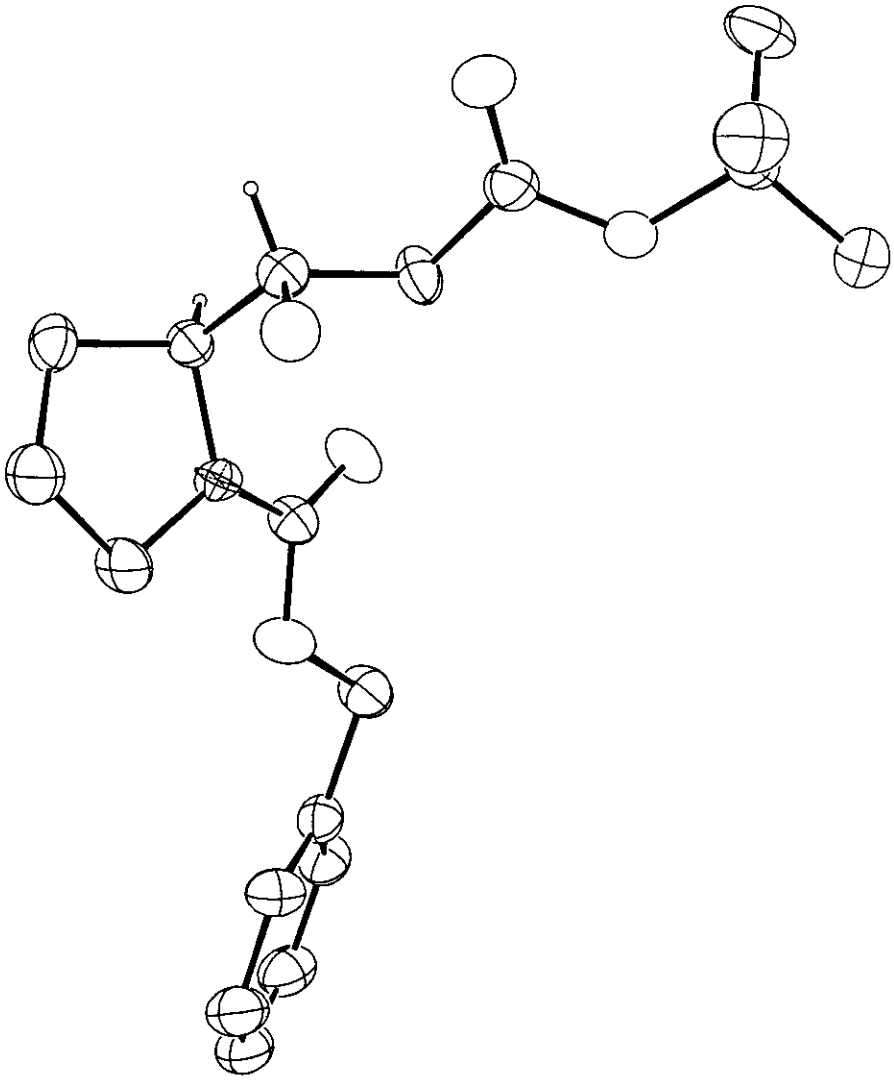


Figure 2

resulting amine with Boc-L-valine mediated by DCC and HOBT gave 20 in 82% yield. Compound 20 was converted to depsipeptide 21 by reaction with N-benzyloxycarbonyl-L-phenylalanine, DCC and DMAP in methylene chloride.

All attempts to convert the S,R isomer 19b to 21 by removal of the benzyloxycarbonyl group, followed by incorporation of Boc-L-valine and esterification with Z-L-phenylalanine, under Mitsunobu conditions,[15] were unsuccessful. Compound 21 served as the common intermediate for the synthesis of detoxin B1 and B3. Removal of the benzyloxycarbonyl group in 21, followed by acylation with acetyl chloride, afforded 22 in 82% yield for the two steps. Acylation with isobutyric acid yielded 23 in 90% yield. Compounds 22 and 23 were converted to detoxin B1 (1) and B3 (2) respectively by removal of both the Boc group and ester functionality using trimethylsilyl chloride and sodium iodide.[16] The ^{13}C nmr spectra of the synthetic detoxins were in good agreement with the values reported for the natural products.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Bruker WM 250 (250 MHz) Fourier transform spectrometer. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Infrared spectra (ir) were run on a Perkin-Elmer Model 281A or 281B spectrometers. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60F-254 plates (250μl). Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid, and phosphomolybdic acid reagent (7% w/v) in 95% ethanol. Chromatography was carried out on E. Merck silica gel 60 (particle size 0.040-0.063 mm) using the solvent systems listed under the individual experiments, and under a slightly positive pressure. Elemental analyses were performed by Mic Anal Organic Microanalysis labs, Tucson, AZ. Optical rotations were recorded on a Perkin-Elmer Model 241 Polarimeter, at the sodium D line, and ambient temperatures. High resolution mass spectra (HRMS) were obtained on a Hitachi-Perkin Elmer RMH-2 high resolution, double focusing, electron impact spectrometer or a vacuum generator's V.G. 707H spectrometer interfaced with a Kratos DS-50-S data system.

All solvents used were reagent grade. Anhydrous ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone; methylene chloride and N,N-dimethylformamide (DMF) were distilled from calcium hydride.

Methyl N-(tert-butyloxycarbonyl)-L-prolinate (5). Method A. To a cooled solution of L-proline (11.5 g; 0.1 M) in methanol (100 ml), freshly distilled thionyl chloride (8.1 ml; 0.11 mM) was

added dropwise with stirring. The reaction mixture was stirred at ambient temperature for 2 h, and refluxed for 1½ h. The solvent was removed in vacuo, methanol (3 x 20 ml) was added to the residue, followed by evaporation in vacuo. After storage at 0°C for 24-36 h, the oily product slowly crystallized. It was triturated with anhydrous ether to afford 16.5 g (100% yield) of the hydrochloride salt of methyl L-prolinate (4) as a very hygroscopic solid, mp 69-70°C (lit.[4] mp 71°C). Compound 4 was dissolved in methylene chloride (120 ml) and the solution cooled to 0°C. Triethylamine (28 ml; 0.2 M) and di-tert-butyl dicarbonate (26.2 g; 0.12 M) were then added. The reaction mixture was stirred at 0° for 1 h and room temperature overnight. It was then made acidic with saturated citric acid solution. The methylene chloride layer was washed with water, saturated sodium bicarbonate solution, saturated sodium chloride solution, and dried (Na_2SO_4). Removal of the drying agent and concentration of the solvent were followed by purification of the crude material by flash chromatography using hexane:acetone (85:15) as eluant to afford product 5 as a colorless oil (22.0 g; 96% yield); $[\alpha]_D^{24}$ -54.37° (c 3.67 , $CHCl_3$) [lit.[3] $[\alpha]_D^{25}$ - 54.54° (c 10.04, $CHCl_3$)]; ir (neat) 1750 (ester), 1700 (Boc) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.51 and 1.56 (9H, s, Boc), 1.81-2.09 (3H, m), 2.13-2.4 (1H, m), 3.35-3.65 (2H, m, $-CH_2-N$), 3.82 (3H, s, $-COOCH_3$) and 4.3 (1H, two sets of d, J=6 Hz).

Method B. To a cooled solution of L-proline (2.3 g; 20 mM) in dioxane (16 ml), water (8 ml) and 1N NaOH (42 ml), di-tert-butyl dicarbonate (4.8 g; 22 mM) was added with stirring. Stirring was continued at 0°C for 1 h and at room temperature overnight. The reaction mixture was then made acidic with a saturated citric acid solution and then extracted with ethyl acetate (2 x 70 ml). The ethyl acetate layer was dried (Na_2SO_4) and concentrated. The resulting pale yellow syrup of Boc-proline (6) was dissolved in methylene chloride (40 ml) and methanol (4 ml) and cooled to 0°C. Dicyclohexylcarbodiimide (4.95 g; 24 mM) and dimethylaminopyridine (1.22 g; 10 mM) were then added. The reaction mixture was stirred at 0°C for 2 h and at room temperature overnight. The dicyclohexyl urea was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in ethyl acetate-water (70 ml each). The ethyl acetate layer was washed with saturated sodium carbonate solution, saturated sodium chloride solution, dried (Na_2SO_4), and concentrated. Purification by chromatography as before afforded 3.364 g (73.45% yield) of product, identical in all respects to the sample prepared earlier.

N-(tert-Butyloxycarbonyl)-L-prolinol (7). To a stirred suspension of lithium chloride (0.6825 g; 16.17 mM) and sodium borohydride (0.6089 g; 16.09 mM) in ethanol (11.5 ml), at 0°C under nitrogen, a solution of 5 (1.843 g; 8.05 mM) in dry THF (8 ml) was added dropwise. The reaction mixture was stirred at ambient temperature for 4 h. The precipitate formed was removed by filtration and washed with ethanol (5 ml). The filtrate and the washings were concentrated

in vacuo to dryness. The residue was extracted with ethyl acetate and the organic layer was washed with saturated sodium chloride solution, and dried (Na_2SO_4). Concentration of the solution followed by flash chromatography of the crude material using hexane:acetone (80:20) as eluant afforded product 7 (1.4940 g; 92.4% yield); mp 60-62°C; $[\alpha]_D^{24}$ -48.83° (c 1.2, $CHCl_3$); ir ($CHCl_3$) 3400, 3000, 1675, 1420, 1380, 1250, 1180 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.48 (9H, s, Boc), 1.65-1.87 (2H, m), 1.9-2.04 (2H, m), 3.2-3.47 (2H, m, -O-CH_2-), 3.51-3.67 (2H, m, -N-CH_2-), 3.9-4.06 (1H, m) and 4.83 (1H, br s, -OH, D_2O exchangeable).

Ethyl (βS, 2S)-1-(tert-butyloxycarbonyl)-2-pyrrolidinehydracrylate (9a). To a stirred solution of methylene chloride (22 ml) and DMSO (1.1 ml; 15.5 mM) in a 100 ml flame-dried flask, at -78°C under a nitrogen atmosphere, was added dropwise oxalyl chloride (0.9 ml; 10.32 mM). This mixture was allowed to stir for 10 min at which time 7 (1.0 g; 4.98 mM) in methylene chloride (10 ml) was added dropwise. The resulting mixture was stirred at -78°C for 20 min followed by addition of triethylamine (2.8 ml; 20.1 mM). The reaction mixture was then warmed to room temperature, treated with water (5 ml) and the two layers formed were separated. The aqueous layer was saturated with sodium chloride and extracted with methylene chloride (1 x 25 ml) and ethyl acetate (3 x 5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude aldehyde 8 contaminated with a white precipitate which was removed by filtration and washed with ether:petroleum ether (1:4). Subsequent concentration of the filtrate afforded the crude aldehyde quantitatively. This compound was not purified but was immediately transferred to a 100 ml flask and azeotropically dried with benzene (3 x 20 ml). To the aldehyde in ether (25 ml), under nitrogen, a zinc-copper couple (1.14 g; 17.44 mM, 3.3% copper in zinc) was added with stirring. To this mixture, ethyl bromoacetate (2.22 ml; 20.02 mM) and a few crystals of iodine were added, and the reaction mixture was refluxed for 45 min. It was then allowed to cool to room temperature and ether (30 ml) and 5% aqueous HCl (30 ml) were added. The ether layer was washed with 5% aq. $NaHCO_3$ (5 ml), and the combined aqueous layers were saturated with sodium chloride and extracted with ethyl acetate (3 x 25 ml). The organic layer was dried (Na_2SO_4), concentrated, and the residue purified by column chromatography using ethyl acetate:methylene chloride (1:4) as eluant to give a mixture of 9a and 9b (1.21 g; 85% yield from 7) as a colorless oil. The diastereomers were separated by column chromatography using ethyl acetate:methylene chloride (1:19) as eluant. Compound 9a: $[\alpha]_D^{26}$ -58.54° (c 1.58, MeOH); ir (neat): 3450, 3000, 1750, 1680, 1400, 1180, 920, 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.27 (3H, t, J=7.1 Hz), 1.47 (9H, s), 1.70-2.08 (4H, m), 2.35-2.52 (2H, m), 3.20-3.35 (1H, m), 3.44-3.60 (1H, m), 3.85-4.00 (1H, m), 4.17 (4H, m and q, J=7.1 Hz). Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.39; H, 8.68; N, 4.74. Compound

9b: $[\alpha]_D^{26}$ -58.94° (c 1.04, MeOH); ^{1}H nmr ($CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.50 (9H, s), 1.62-2.10 (4H, m), 2.34-2.60 (2H, m), 3.20-3.40 (1H, m), 3.42-3.60 (1H, m), 3.90-4.10 (2H, m), 4.20 (2H, q, J=7.1 Hz), 4.90-5.10 (1H, m). This compound had the same ir and analytical data as 9a. When the Reformatsky reaction was carried out on aldehyde 8 using methyl bromoacetate under the conditions described above, 10a and 10b were obtained in 87% yield. Compound 10a: $[\alpha]_D^{22}$ -31.75° (c 1.03, $CHCl_3$); ir (neat): 3460, 2980, 1740, 1680, 1410, 1380, 1260, 1170, 1110, 770 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.47 (9H, s), 1.68-2.12 (4H, m), 2.34-2.55 (2H, m), 3.20-3.34 (1H, m), 3.44-3.60 (1H, m), 3.71 (3H, s), 3.75-4.04 (1H, m), 4.15-4.24 (1H, m), 4.54-4.70 (1H, br s); HRMS, M^+ calc for $C_{13}H_{23}NO_5$: 273.1575. Found: 273.1589. Compound 10b: $[\alpha]_D^{22}$ -62.69° (c 4.17, $CHCl_3$); ^{1}H nmr ($CDCl_3$) δ 1.46 (9H, s), 1.58-2.10 (4H, m), 2.35-2.60 (2H, m), 3.22-3.38 (1H, m), 3.38-3.60 (1H, m), 3.71 (3H, s), 3.90-4.22 (2H, m), 5.00-5.20 (1H, br s). Compounds 10a and 10b have the same ir and mass spectra.

Reduction of aldehyde 8 to alcohol 7. A solution of aldehyde 8 (obtained by the oxidation of 0.52 g of 7) in ethanol (15 ml) was added dropwise to a solution of sodium borohydride (0.1188 g; 3.14 mM) in ethanol (16 ml) at 0°C. The mixture was stirred at 0°C for 15 min and at ambient temperature for 2 h. Acidification with 5% HCl to pH 3 followed by extractive work up and purification by flash chromatography afforded 7 (0.37 g; 71% yield) which had $[\alpha]_D^{23}$ -48.75° (c 1.43, $CHCl_3$) compared to the standard value $[\alpha]_D^{24}$ -48.83° (c 1.2, $CHCl_3$).

(βS,2S)-1-Carboxy-2-pyrrolidinehydracrylic acid, 1-tert-butyl-2-ethyl ester (ester with N-carboxy-3-phenyl-L-alanine N-benzyl) (11). A mixture of 9a (0.445 g; 1.55 mM) and N-benzyloxycarbonyl-L-phenylalanine (0.56 g; 1.87 mM) was azeotropically dried with benzene (3 x 10 ml). To this mixture, in methylene chloride (8 ml), at 0°C with stirring, DCC (0.32 g; 1.55 mM) and dimethylaminopyridine (0.02 g; 0.16 mM) were added sequentially. The reaction mixture was stirred at 0°C for 1 h and at room temperature for 12 h. The solvent was removed in vacuo, the residue redissolved in ethyl acetate (30 ml), and then washed sequentially with 5% aqueous HCl (1 x 2 ml) and 50% aqueous K_2CO_3 (1 x 2 ml). The combined aqueous layers were saturated with sodium chloride and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification by column chromatography using ether: petroleum ether (1:1) as the eluant gave 11 (0.76 g; 86% yield) as a low melting solid; $[\alpha]_D^{26}$ -23.65° (c 1.81, $CHCl_3$); ir 3360, 3000, 1735, 1690, 1610, 1510, 1410, 1180, 920, 750 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.50 (9H, s), 1.6-2.00 (4H, m), 2.40-2.70 (2H, m), 2.9-3.6 (4H, m), 3.8-4.0 (2H, m), 4.10 (2H, q, J=7.1 Hz), 4.60 (1H, m), 5.0 (2H, s) and 5.2 (1H, br s) 7.08-7.50 (10H, m); Anal. Calcd. for $C_{31}H_{40}N_2O_8$: C, 65.48; H, 7.09; N, 4.93. Found: C, 65.83; H, 7.17; N, 4.77. Compound 12 was obtained in 90% yield

from 10a as a low melting solid; $[\alpha]_D^{20}$ -20.71° (c 4.07, $CHCl_3$); ir ($CHCl_3$): 3440, 3020, 2980, 1730, 1690, 1300, 1400, 1170 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.46 (9H, s), 1.62-1.92 (4H, m), 2.40-2.70 (2H, m), 2.90-3.54 (4H, m), 3.65 (s, 3H); 3.80-4.05 (1H, m), 4.57 (1H, m), 5.06 (2H, s), 5.27 (1H, d, J = 7.9 Hz), 5.50-5.68 (1H, m), 7.08-7.48 (10H, m); HRMS, M^+ calcd for $C_{30}H_{38}N_2O_8$: 554.2625. Found: 554.2614.

(βS, 2S)-1-[(S)-N-Carboxyvalyl]-2-pyrrolidinehydracrylic acid, N-tert-butyl 2-ethyl ester, ester with N-carboxy-3-phenyl-L-alanine N-benzyl ester (13). To a solution of 11 (0.127 g; 0.223 mM) in methylene chloride (0.5 ml) at 0°C, trifluoroacetic acid (0.5 ml; 6.5 mM) was added. The reaction mixture was allowed to warm to ambient temperature and then stirred for 5 min. The solvents were removed in vacuo. Traces of trifluoroacetic acid were removed by azeotroping the residue with ether (3 x 10 ml) followed by drying it under reduced pressure (5 mm Hg) for 2 h. The crude trifluoroacetate salt was dissolved in methylene chloride (1.1 ml), cooled to 0°C, and triethylamine (0.1 ml; 0.717 mM) was added. The solution was stirred at 0°C for 10 min, and Boc-L-valine (0.060 g; 0.276 mM), DCC (0.060 g; 0.291 mM) and HOBT (0.040 g; 0.296 mM) were added sequentially. The reaction mixture was stirred at 0°C for 1 h and at room temperature for 12 h. The solvent was removed in vacuo and the residue redissolved in ethyl acetate and sequentially washed with 5% aqueous HCl (1 x 2 ml) and 50% aqueous K_2CO_3 (1 x 2 ml). The combined aqueous layers were saturated with sodium chloride, extracted with ethyl acetate (3 x 20 ml), and the extracts dried (Na_2SO_4), and concentrated. Purification by column chromatography using ethyl acetate: methylene chloride (1:9) as eluant gave 13 (0.133 g; 90% yield from 11) as a low melting solid; $[\alpha]_D^{22}$ -36.74° (c 0.89, $CHCl_3$); ir 3460, 3420, 3000, 1730, 1650, 1510, 1440, 1040, 760 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82 (3H, d, J=6.7 Hz), 0.91 (3H, d, J=6.8 Hz), 1.24 (3H, t, J=7.1 Hz), 1.42 (9H, s), 1.60-2.10 (5H, m), 2.44-2.55 (2H, m), 2.93 (1H, dd, J=7.4 and 14.1 Hz), 3.09 (1H, dd, J=6.2 and 14.1 Hz), 3.35-3.55 (1H, m), 3.60-3.75 (1H, m), 4.1 (2H, q, J=7.1 Hz), 4.2-4.3 (2H, m), 4.45-4.60 (1H, m), 5.0 (2H, s), 5.10-5.35 (2H, m), 5.60-5.80 (1H, m), 7.10-7.40 (10H, m); HRMS, $M^+ + 1$ calcd. for $C_{36}H_{49}O_9N_3$: 668.3547. Found: 668.3505. Compound 14 was obtained in 80% yield from 12 as a white solid; mp 47-50°C; $[\alpha]_D^{24}$ -38.78° (c 1.88, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 0.81 (3H, d, J = 6.7 Hz), 0.91 (3H, d, J = 6.8 Hz), 1.42 (9H, s), 1.72-2.10 (5H, m), 2.49 (2H, d, J = 7.2 Hz), 2.94 (1H, dd, J = 14.0 and 7.5 Hz), 3.08 (1H, dd, J = 14.0 and 6.4 Hz), 3.40-3.50 (1H, m), 3.60-3.80 (4H, s and m), 4.20-4.35 (2H, m), 4.48-4.60 (1H, m), 5.00-5.20 (2H, m), 5.20-5.35 (2H, m), 5.65-5.80 (1H, m), 7.10-7.50 (10H, m); HRMS, M^+ calcd for $C_{35}H_{47}N_3O_9$: 653.3301. Found: 653.3267.

(βS,2S)-1-[(S)-N-Carboxyvalyl]-2-pyrrolidinehydracrylic acid, N-tert-butyl 2-ethyl ester, ester with N-acetyl-3-phenyl-L-alanine (15). A mixture of compound 13 (0.614 g; 0.921 mM), ethanol

(8 ml), and 10% palladium on carbon (0.184 g) was hydrogenated (60 psi) at room temperature in a Parr hydrogenator for 12 h. It was then filtered through Celite, and the catalyst was washed with ethanol (3 x 20 ml) and ethyl acetate (3 x 20 ml). The filtrate was concentrated in vacuo to afford the crude amine quantitatively as a colorless oil. To a stirred solution of the amine in pyridine (9.21 ml; 113.87 mM) and methylene chloride (3.1 ml), at 0°C, acetyl chloride (0.11 ml; 1.55 mM) was added. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 12 h. Solvents were removed in vacuo, and the crude product was purified by column chromatography using ether: petroleum ether (1:3) as eluant. This afforded pure product 15 (0.423 g; 80% yield from 13) as a low melting solid; $[\alpha]_D^{22}$ -29.0° (c 1.3, $CHCl_3$); ir 3400, 3000, 1740, 1650, 1510, 1440, 1380, 1180, 760 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82 (3H, d, J=6.7 Hz), 0.91 (3H, d, J=6.8 Hz), 1.24 (3H, t, J=7.1 Hz), 1.42 (9H, s), 1.70-2.10 (8H, m and s), 2.45-2.60 (2H, m), 2.93 (1H, dd, J=7.3 and 14.0 Hz), 3.09 (1H, dd, J=6.6 and 14.0 Hz), 3.40-3.55 (1H, m), 3.60-3.75 (1H, m), 4.10 (2H, q, J=7.1 Hz), 4.20-4.35 (2H, m), 4.65-4.80 (1H, m), 5.25 (1H, d, J=9.2 Hz), 5.68-5.78 (1H, m), 5.90 (1H, d, J=7.8 Hz), 7.10-7.40 (5H, m), HRMS, M^+ + 1 calcd. for $C_{30}H_{45}N_3O_8$: 576.3285. Found: 576.3210. Compound 16 was obtained in 70% yield from 14 as a low melting solid; $[\alpha]_D^{24}$ -33.02° (c 2.12, $CHCl_3$); ir ($CHCl_3$): 3450, 3030, 3000, 1745, 1710, 1680, 1640, 1500, 1440, 1370, 1170 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82 (3H, d, J=6.7 Hz), 0.93 (3H, d, J = 6.7 Hz), 1.42 (9H, s), 1.75-2.10 (8H, m and s), 2.49 (2H, d, J = 6.9 Hz), 2.80 (1H, dd, J = 14.1 and 6.9 Hz), 3.07 (1H, dd, J = 14.1 and 6.6 Hz), 3.40-3.54 (1H, m), 3.60-3.75 (1H, m), 3.66 (3H, s), 4.20-4.32 (2H, m), 4.65-4.80 (1H, m), 5.28 (1H, d, J = 11.1 Hz), 5.65-5.75 (1H, m), 6.03 (1H, d, J = 7.6 Hz), 7.14-7.44 (5H, m); HRMS, M^+ calcd for $C_{29}H_{43}O_8N_3$: 561.3047. Found: 561.2990.

tert-Butyl (βS,2S)-1-(benzyloxycarbonyl)-2-pyrrolidinehydracrylate (19a). To a stirred solution of methylene chloride (20 ml) and DMSO (0.9 ml; 12.68 mM) in a 100 ml flame-dried flask, at -78°C under a nitrogen atmosphere, was added dropwise oxalyl chloride (0.74 ml; 8.48 mM). This mixture was allowed to stir for 10 min at which time N-benzyloxycarbonyl-L-prolinol (17) (0.99 g; 4.21 mM) in methylene chloride (9 ml) was added dropwise. The resulting mixture was stirred at -78°C for 20 min followed by addition of triethylamine (2.35 ml; 16.86 mM). The reaction mixture was then warmed to room temperature, treated with water (5 ml), and the two layers formed were separated. The aqueous layer was saturated with sodium chloride and extracted with methylene chloride (1 x 25 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude aldehyde (18) with a white precipitate which was removed by filtration and washed with ether:petroleum ether (1:4). Subsequent concentration of the filtrate gave the crude aldehyde quantitatively. This compound was not further purified but

was immediately transferred to a 100 ml flask and azeotropically dried with toluene (2 x 20 ml). To the aldehyde in ether (20 ml) under nitrogen, a zinc-copper couple (1.00 g; 15.30 mM, 3.3% copper in zinc) was added with stirring. To this mixture, tert-butyl bromoacetate (2.73 ml; 16.91 mM) was added via a syringe. The reaction mixture was heated to reflux, and a few crystals of iodine were added (3 x at 30 min intervals). During this time, the Zn-Cu couple was also broken up manually with an oven-dried spatula. At the end of 1.5 h of reaction time, additional Zn-Cu couple (0.5 g; 7.65 mM) and tert-butyl bromoacetate (1.4 ml; 8.67 mM) were added along with a few more crystals of iodine. After another 2 h of refluxing, the reaction was cooled, diluted with ether (50 ml), and washed sequentially with 5% aqueous HCl (15 ml) and 5% aqueous $NaHCO_3$ (15 ml). The combined aqueous layers were saturated with NaCl and extracted with ethyl acetate (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography using ethyl acetate: methylene chloride (1:2) as eluant to give a separable mixture of 19a and 19b (1.18 g; 80% yield from 17) as a colorless oil. The diastereomers were separated by column chromatography on silica gel using ethyl acetate:methylene chloride (1:19) as eluant to give 19a and 19b as white crystalline solids. Compound 19a: mp 75-77°C; $[\alpha]_D^{23}$ -31.67° (c 0.54, $CHCl_3$); ir ($CHCl_3$): 3440, 3000, 1700, 1420, 1360, 1160 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.46 (9H, s), 1.71-2.10 (4H, m), 2.32-2.45 (2H, m), 3.32-3.45 (1H, m), 3.52-3.65 (1H, m), 3.80-4.35 (2H, m), 4.80-4.90 (1H, m), 5.15 (2H, s), 7.20-7.48 (5H, m); HRMS, M^+ calc for $C_{19}H_{27}NO_5$: 349.1887. Found: 349.1874. Compound 19b: mp 101-103°C; $[\alpha]_D^{21}$ -59.18° (c 0.61, $CHCl_3$); ^1H nmr ($CDCl_3$) δ 1.46 (9H, s), 1.71-2.05 (4H, m), 2.28-2.54 (2H, m), 3.30-3.45 (1H, m), 3.50-3.65 (1H, m), 3.95-4.3 (2H, m), 5.14 (2H, s), 7.28-7.48 (5H, m). This compound had the same ir and mass spectra as 19a.

(8S,2S)-1-[(S)-N-Carboxyvalyl]-2-pyrrolidinehydracrylic acid, N-tert-butyl-2-tert-butyl ester (20). A mixture of compound 19a (0.495 g; 1.42 mM), ethanol (6.5 ml), and 10% palladium on carbon (0.3 g) was hydrogenated (60 psi) at room temperature in a Parr hydrogenator for 12 h. The catalyst was removed by filtration through Celite and washed with ethanol (3 x 20 ml). The filtrate was concentrated in vacuo to afford the crude amine quantitatively as a colorless oil which was azeotropically dried with toluene (2 x 10 ml). To a stirred solution of the amine in methylene chloride (7.5 ml) at 0°C, was added sequentially Boc-L-valine (0.31 g; 1.43 mM), DCC (0.30 g; 1.45 mM), and HOBT (0.20 g; 1.48 mM). The reaction mixture was stirred at 0°C for 1 h and at room temperature for 12 h. The solvent was then removed in vacuo and the residue redissolved in ethyl acetate (30 ml) and cooled to 0°C. After filtration of the precipitated urea, followed by washing with ethyl acetate (3x 20 ml), the filtrate was washed sequentially with 5% aqueous HCl (1 x 2 ml) and 5% aqueous $NaHCO_3$ (1 x 2 ml). The organic layer was dried

(Na_2SO_4) and concentrated to afford crude 20. Purification by chromatography using ethyl acetate:methylene chloride (1:4) as the eluant gave pure 20 (0.482 g; 82% yield from 19) as a low melting white solid; $[\alpha]_D^{26}$ -31.69° (c 0.65, $CHCl_3$); ir ($CHCl_3$): 3460, 3100, 2960, 1740, 1640, 1520, 1450, 1380, 1250, 1170 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.93 (3H, d, J = 6.7 Hz), 1.01 (3H, d, J = 6.8 Hz), 1.45 (18H, s), 1.80-2.05 (5H, m), 2.20-2.32 (2H, m), 3.38-3.58 (1H, m), 3.78-3.90 (1H, m), 4.10-4.22 (2H, m), 4.28-4.40 (2H, m), 5.30 (1H, d, J = 12.1 Hz); HRMS, M^+ calc for $C_{21}H_{38}N_2O_6$: 414.2727. Found: 414.2762.

(8S, 2S)-1-Carboxy-2-pyrrolidinehydracrylic acid, 1,2-di-tert-butyl ester, ester with N-carboxy-3-phenyl-L-alanine N-benzyl ester (21). To a solution of 20 (0.44 g; 1.06 mM), which had been azeotropically dried with toluene (2 x 15 ml), in 5.5 ml of methylene chloride stirring at 0°C was added sequentially N-benzyloxycarbonyl-L-phenylalanine (0.48 g; 1.60 mM), DCC (0.33 g; 1.60 mM), and dimethylaminopyridine (0.02 g, 0.16 mM). The reaction was warmed to room temperature and stirred for 12 h. The solvent was removed in vacuo, and the residue redissolved in ethyl acetate (30 ml) and cooled to 0°C. After filtration of the mixture and washing of the precipitated urea with ethyl acetate (3 x 20 ml), the filtrate was washed sequentially with 5% aqueous HCl (1 x 5 ml) and 5% aqueous $NaHCO_3$ (1 x 5 ml). The organic layer was dried (Na_2SO_4) and concentrated. Purification by column chromatography using ethyl acetate: methylene chloride (1:9) as eluant gave 21 (0.67 g; 90% yield) as a white solid; mp 46-50°C; $[\alpha]_D^{19}$ -32.18° (c 3.63, $CHCl_3$), ir ($CHCl_3$): 3440, 3000, 1720, 1640, 1500, 1430, 1370, 1160 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.82 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.8 Hz), 1.45 (18H, s), 1.75-2.10 (5H, m), 2.35-2.54 (2H, m), 2.92 (1H, dd, J = 7.5 and 14.1 Hz), 3.10 (1H, dd, J = 6.2 and 14.1 Hz), 3.38-3.52 (1H, m), 3.60-3.74 (1H, m), 4.20-4.35 (2H, m), 4.45-4.60 (1H, m), 5.04 (2H, d, J = 4.4 Hz), 5.20-5.35 (2H, m), 5.65-5.78 (1H, m), 7.14-7.45 (10H, m); Anal. Calcd for $C_{38}H_{53}O_9N_3$: C, 65.58; H, 7.69; N, 6.04. Found: C, 65.53; H, 7.73; N, 5.99.

(8S,2S)-1-[(S)-N-Carboxyvalyl]-2-pyrrolidinehydracrylic acid, N-tert-butyl 2-tert-butyl ester, ester with N-acetyl-3-phenyl-L-alanine (22). A mixture of compound 21 (0.308 g; 0.443 mM), ethanol (4.25 ml), and palladium on carbon (0.2 g) was hydrogenated (60 psi) at room temperature in a Parr hydrogenator for 12 h. It was then filtered through Celite, and the catalyst was washed with ethanol (3 x 15 ml). The filtrate was concentrated in vacuo to afford the crude amine quantitatively as a colorless oil which was azeotropically dried with toluene (2 x 15 ml). To a stirred mixture of the crude amine in methylene chloride (2.2 ml) at 0°C was added dimethylaminopyridine (0.22 g; 1.80 mM) and acetyl chloride (0.07 ml, 0.98 mM). The reaction was stirred at ambient temperature for 6 h. It was then diluted with methylene chloride (20 ml), and washed sequentially with 5% aqueous HCl and 5% aqueous $NaHCO_3$. The organic

layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate:methylene chloride (1:2) as eluant to afford 22 (0.216 g; 82% from 21) as a white low melting solid. Compound 22: $[\alpha]_D^{22}$ -26.25° (c 0.88, $CHCl_3$); ir ($CHCl_3$): 3460, 3000, 1750, 1720, 1690, 1650, 1510, 1435, 1380, 1170, 915 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.83 (3H, d, J = 6.7 Hz), 0.93 (3H, d, J = 6.8 Hz), 1.43 (18H, s), 1.70-2.10 (8H, m and s), 2.40-2.54 (2H, m), 2.94 (1H, dd, J = 6.7 and 14.2 Hz), 3.10 (1H, dd, J = 6.3 and 14.2 Hz), 3.40-3.54 (1H, m), 3.58-3.72 (1H, m), 4.20-4.35 (2H, m), 4.65-4.75 (1H, m), 5.28 (1H, d, J = 9.1 Hz), 5.65-5.78 (1H, m), 5.91 (1H, d, J = 7.6 Hz), 7.10-7.45 (5H, m); HRMS, M^+ calcd. for $C_{32}H_{49}N_3O_8$: 603.3516. Found: 603.3494.

(βS,2S)-1-[(S)-N-Carboxyvalyl]-2-pyrrolidinehydracrylic acid, N-tert-butyl-2-tert-butyl ester, ester with N-isobutyryl-3-phenyl-L-alanine (23). A mixture of compound 21 (0.285 g, 0.41 mM), ethanol (4.25 ml), and palladium on carbon (0.2 g) was hydrogenated (60 psi) at room temperature in a Parr hydrogenator for 12 h. It was then filtered through Celite, and the catalyst was washed with ethanol (3 x 15 ml). The filtrate was concentrated in vacuo to afford the crude amine quantitatively as a colorless oil which was azeotropically dried with toluene (2 x 15 ml). To a stirred mixture of the crude amine, in methylene chloride (2.5 ml) at 0°C, was added sequentially isobutyric acid (0.06 ml, 0.65 mM), DCC (0.13 g; 0.63 mM), and HOBT (0.09 g; 0.67 mM). The reaction was then stirred at room temperature for 12 h. The solvent was removed, the residue diluted with ethyl acetate (20 ml) and cooled to 0°C. After filtration of the reaction mixture and washing of the precipitated urea with ethyl acetate (3 x 15 ml), the filtrate was washed sequentially with 5% aqueous HCl and 5% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate:methylene chloride (1:4) as eluant to give 23 (0.232 g, 90% yield from 21) as a low melting white solid. Compound 23: $[\alpha]_D^{23}$ -30.55° (c 1.83, $CHCl_3$); ir ($CHCl_3$): 3460, 3000, 1760, 1740, 1685, 1650, 1510, 1430, 1400, 1380, 1250, 1160 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.83 (3H, d, J = 6.7 Hz), 0.91 (3H, d, J = 6.8 Hz), 1.03-1.21 (6H, m), 1.43 (18H, s), 1.80-2.10 (4H, m), 2.25-2.68 (4H, m), 2.94 (1H, dd, J = 6.7 and 14.2 Hz), 3.10 (1H, dd, J = 6.3 and 14.2 Hz), 3.40-3.52 (1H, m), 3.60-3.74 (1H, m), 4.20-4.35 (2H, m), 4.60-4.75 (1H, m), 5.36 (1H, J = 9.3 Hz), 5.70-5.80 (1H, m), 5.90 (1H, d, J = 7.6 Hz), 7.14-7.38 (5H, m); HRMS, M^+ calcd. for $C_{34}H_{53}N_3O_8$: 631.3853. Found: 631.3859.

Detoxin B1 (1). To a stirred solution of compound 22 (0.108 g; 0.179 mM) (azeotropically dried with benzene, 2 x 5 ml) in acetonitrile (1.8 ml) was added chlorotrimethylsilane (0.1 ml; 0.79 mM) and sodium iodide (0.11 g; 0.73 mM). The reaction was stirred at 50°C for 1 h and then cooled to room temperature. It was then diluted with ethyl acetate (60 ml) and washed with 5%

aqueous $Na_2S_2O_3$ (5 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate:methanol (1:0, 1:1, 0:1) as an eluant gradient system to give 1 (0.0456 g, 57% yield) as a white solid. Compound 1: mp > 170°C (d); $[\alpha]_D^{21}$ -42.87° (c 0.87, MeOH); ir (KBr): 3300, 3050, 3000, 2980, 1755, 1670, 1600, 1450, 1400, 1200, 710 cm^{-1}; ^1H nmr (MeOH-d_4) δ 0.96 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 7.0 Hz), 1.82-2.25 (8H, m and s), 2.40-2.68 (2H, m), 2.85 (1H, dd, J = 9.9 and 14.2 Hz), 3.09 (1H, dd, J = 5.3 and 14.2 Hz), 3.44-3.70 (2H, m), 4.05 (1H, d, J = 3.2 Hz), 4.20-4.34 (1H, m), 4.50-4.65 (1H, m), 5.80-5.94 (1H, m), 7.15-7.40 (5H, m); ^{13}C nmr (MeOH-d_4): δ 17.62, 20.42, 22.73, 25.34, 26.43, 31.52, 38.98, 41.49, 55.78, 58.79, 60.99, 74.05, 128.34, 129.96, 130.59, 138.70, 171.58, 172.89, 173.33, 177.79; HRMS, M^+ calcd for $C_{23}H_{33}N_3O_6$: 447.2366. Found: 447.2318.

Detoxin B3 (2). To a stirred solution of compound 23 (0.107 g; 0.171 mM) (azeotropically dried with benzene, 2 x 5 ml) in acetonitrile (1.7 ml) was added chlorotrimethylsilane (0.09 ml; 0.71 mM) and sodium iodide (0.11 g; 0.73 mM). The reaction was stirred at 50°C for 1.5 h and then cooled to room temperature. It was diluted with ethyl acetate (60 ml) and washed with 5% aqueous $Na_2S_2O_3$ (5 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography using ethyl acetate:methanol (1:0, 1:1, 0:1) as an eluant gradient system to give 3 (0.049 g, 60% yield) as a white solid. Compound 3: mp > 170°C (d); $[\alpha]_D^{27}$ -45.58° (c 2.67, MeOH); ir (KBr): 3320, 3050, 3000, 2900, 1750, 1660, 1600, 1460, 1400, 1200, 940, 710 cm^{-1}; ^1H nmr (MeOH-d_4): δ 0.87-1.09 (14H, m), 1.78-2.18 (4H, m), 2.18-2.50 (4H, m), 2.89 (1H, dd, J = 14.0 and 9.6 Hz), 3.15 (1H, dd, J = 14.0 and 5.6 Hz), 3.40-3.70 (4H, m), 4.24-4.35 (1H, m), 4.55-4.70 (1H, m), 5.72-5.85 (1H, m), 7.15-7.35 (5H, m); ^{13}C nmr (MeOH-d_4): δ 16.74, 19.75, 19.87, 20.35, 25.00, 25.97, 31.52, 35.81, 38.47, 41.12, 54.95, 58.64, 60.86, 73.76, 127.77, 129.44, 130.20, 138.60, 172.57, 173.33, 177.49, 179.72; HRMS, M^+ calcd for $C_{25}H_{37}N_3O_6$: 475.2679. Found: 475.2674.

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REFERENCES

1. (a) K. Kakinuma, N. Otake, and H. Yonehara, Tetrahedron Lett., 1972, 2509. (b) N. Otake, K. Kakinuma, and H. Yonehara, Agr. Biol. Chem., 1973, 37, 2777. (c) H. Yonehara, H. Seto, A. Shimazu, S. Aizawa, T. Hidaka, K. Kakinuma, and N. Otake, Agr. Biol. Chem., 1973, 37, 2771. (d) K. Kakinuma, N. Otake, and H. Yonehara, Agr. Biol. Chem.,

1974, 38, 2529. (e) N. Otake, K. Furihata, K. Kakinuma, and H. Yonehara, J. Antibiotics, 1974, 484. (f) T. Ogita, H. Seto, N. Otake, and H. Yonehara, Agr. Biol. Chem., 1981, 45(11), 2605. (g) N. Otake, T. Ogita, H. Seto, and H. Yonehara, Experientia, 1981, 37, 926. (h) K. Kakinuma, N. Otake, and H. Yonehara, Tetrahedron Lett., 1980, 167.

2. W.R. Ewing, B.D. Harris, K.L. Bhat, and M.M. Joullie', unpublished results.
3. Y. Becker, A. Eisenstadt, and J.K. Stille, J. Org. Chem., 1980, 45, 2145.
4. S. Guttmann, Helv. Chim. Acta, 1961, 44, 721.
5. (a) B. Neises and W. Steglich, Angew. Chem. Int. Ed. Engl., 1978, 17, 552. (b) A. Hassner and V. Alexanian, Tetrahedron Lett., 1978, 4475. (c) M.K. Dhaon, R.K. Olsen, and K. Ramasamy, J. Org. Chem., 1982, 47, 1962.
6. (a) F. Leyendecker, F. Jesser, and D. Laucher, Tetrahedron Lett., 1983, 24(33), 3513. (b) D.A. Evans, J.M. Takacs, and K.M. Hurst, J. Am. Chem. Soc., 1979, 101, 371.
7. Y. Hamada and T. Shioiri, Tetrahedron Lett., 1982, 23, 1193.
8. Y. Hamada and T. Shioiri, Chem. Pharm. Bull., 1982, 30, 1921.
9. A.J. Mancuso and D. Swern, Synthesis., 1981, 165.
10. (a) D.H. Rich, E.T. Sun, and A.S. Boparai, J. Org. Chem., 1978, 43, 3624. (b) W.J. Greenlee, P.L. Allibone, D.S. Perlow, A.A. Patchett, E.H. Ulm, and T.C. Vassil, J. Med. Chem., 1985, 28, 434.
11. (a) M. Gaudemar, Organomet. Chem. Rev. A., 1972, 8, 183. (b) M.W. Rathke, Org. React., 1975, 22, 423. (c) L.R. Krepski, L.E. Lynch, S.M. Heilmann, and J.K. Rasmussen, Tetrahedron Lett., 1985, 26, 981. (d) E. Santaniello, and A. Manzocchi, Synthesis, 1977, 698.
12. (a) J.A. Dale, D.L. Dull, and H.S. Mosher, J. Org. Chem., 1969, 34, 2543. (b) G.R. Sullivan, J.A. Dale, and H.S. Mosher, J. Org. Chem., 1973, 38, 2143.
13. W. König and R. Geiger, Chem. Ber., 1970, 103, 788, 2024, 2041.
14. J. M. Cassal, A. Furst, and W. Meier, Helv. Chim. Acta., 1976, 59, 1917.
15. O. Mitsunobu, Synthesis, 1981, 1.
16. (a) G. A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, J. Org. Chem., 1979, 44, 1247. (b) A. H. Schmidt, Aldrichimica Acta, 1981, 14, 31.

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