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Chiral Synthesis of *C*-Carboxyalkyl Dipeptide Inhibitors of Stromelysin-1 (MMP-3)

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Abstract: Enantioselective alkylation of chiral amide enolates derived from L-prolinol with β-branched chiral iodides afforded good yields of hydroxy amide adducts, which were elaborated in four steps to give *C*-carboxyalkyl dipeptide inhibitors of stromelysin-1 (MMP-3).

Key words: asymmetric synthesis, enantioselection, alkylation, enolates, peptide analogues/mimetics,

INTRODUCTION

The matrix metalloproteinases (MMPs) are a family of zinc-containing and calcium-dependent mammalian proteinases that are capable of degrading the extracellular matrix of connective tissues and basement membranes.[1] They are empirically characterized as metal dependent enzymes in that they contain an essential zinc for catalysis and calcium for stability and maximum activity. The activities of collagenase-1 (MMP-1) and stromelysin-1 (MMP-3) were found to increase in the cartilage of patients with rheumatoid and osteoarthritis, and the activities correlates with the severity of the lesion.[2] In addition, elevated levels of stromelysin-1 in human rheumatoid synovium were also noted.[3,4] Thus stromelysin-1 (MMP-3) appears to be an attractive target for investigation, and inhibiton of this enzyme *in vivo* may have therapeutic potential for the treatment of rheumatoid arthritis and osteoarthritis. A number of *N*-carboxyalkyl dipeptides were disclosed from these laboratories as potent MMP-3 inhibitors.[5-8] Further efforts led to the discovery of *C*-carboxyalkyl dipeptide inhibitors, which were shown to be more potent than the corresponding *N*-carboxyalkyl dipeptides in the mouse pleural cavity assay (PLCAV) when administered orally.[9,10] Compound **1** had a K_i of 68 nM against MMP-3 and an ED_{50} of 32 mg/kg po in the PLCAV assay.[9] The *tert*-butyl group at the P2' position (e.g., **2** and **3**) sterically hindered hydrolysis of the P2'-P3' amide bond and appeared to improve plasma stability and oral absorption.[10] Since **3** was also reported to be one of the most active analogues in this series (K_i = 10 nM vs. MMP-3; ED_{50} of 11 mg/kg po in the PLCAV assay),[10] we chose both **3** and **2** as our target compounds for the synthesis.

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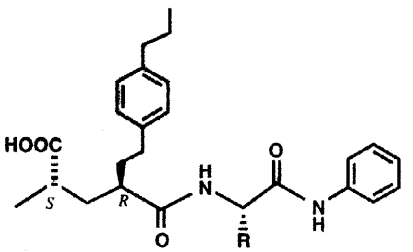
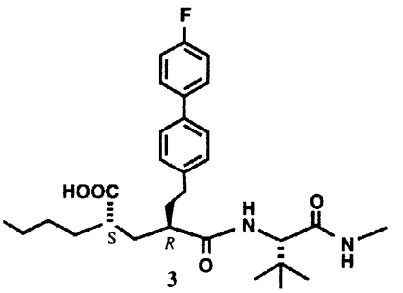


1, R = $CH_2CH(CH_3)_2$
2, R = $C(CH_3)_3$



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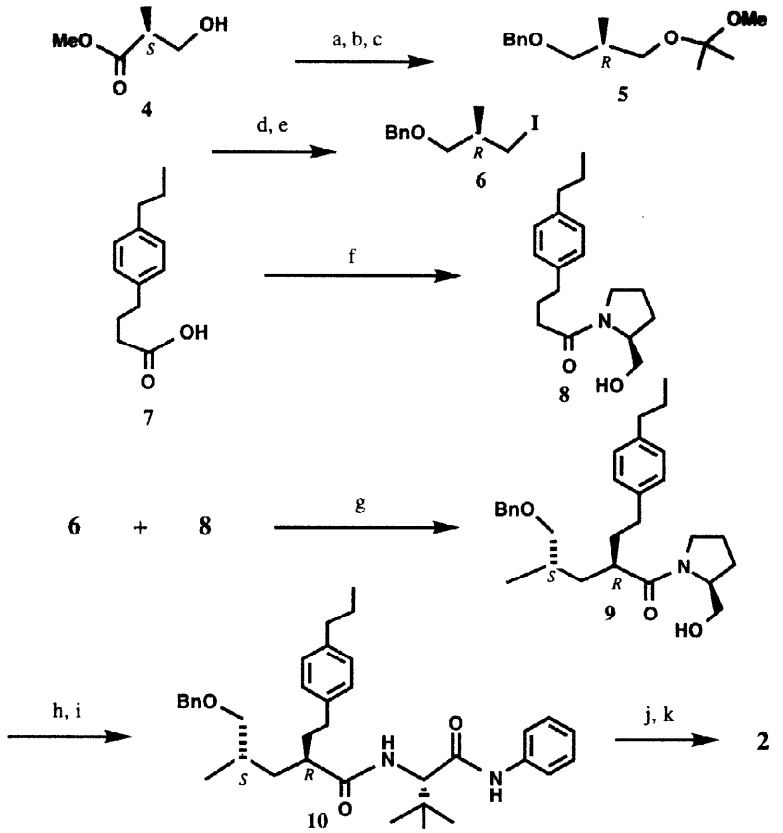
RESULTS AND DISCUSSION

The critical step in the synthesis is the enantioselective alkylation of the chiral amide **8** with benzyl 3-iodo-2(*R*)-methylpropyl ether[11] (**6**). The lithium enolate derived from L-prolinol *N*-propionamide was shown by Evans and co-workers to have sufficient nucleophilicity to react with β-branched alkyl halides with good diastereoselectivity.[12,13] The two substrates **6** and **8** were prepared as outlined in Scheme 1. The iodide **6** was obtained from methyl 3-hydroxy-2(*S*)-methylpropionate (**4**) in five steps in 45% overall yield. The chiral amide **8** was prepared from **7**[9] and L-prolinol in 75% yield. The lithium enolate of **8** in THF was obtained by adding LDA (2 equiv) to **8** at room temperature followed by DMPU (2 equiv) 15 min later. The solution was cooled to -82 °C before adding the electrophile **6**. The coupling product **9** was isolated in 65% yield after flash column chromatography on silica gel. Acid hydrolysis (via N-->O acyl transfer)[12] followed by amide coupling with (*S*)-*tert*-butylglycine phenylamide provided the intermediate **10**. Other amino acids can be used for coupling here to provide derivatives having different P2' and P3' groups. Finally hydrogenolysis with palladium hydroxide on carbon followed by oxidation with Jones' reagent[14] afforded **2** in 68% overall yield in the last two steps. Previous synthesis of *C*-carboxyalkyl dipeptides used the oxazolidinone chiral auxiliary of **7** to selectively introduce *tert*-butoxycarbonylethyl moiety at the 2 position and then formed a dianion with LDA (after oxazolidinone deacylation) for alkylation with methyl iodide or other alkyl halides.[9] This process provided mixtures of diastereomers and required separation by HPLC as their esters.[9] In this synthesis, we obtained an enantiomerically pure product.

Scheme 1

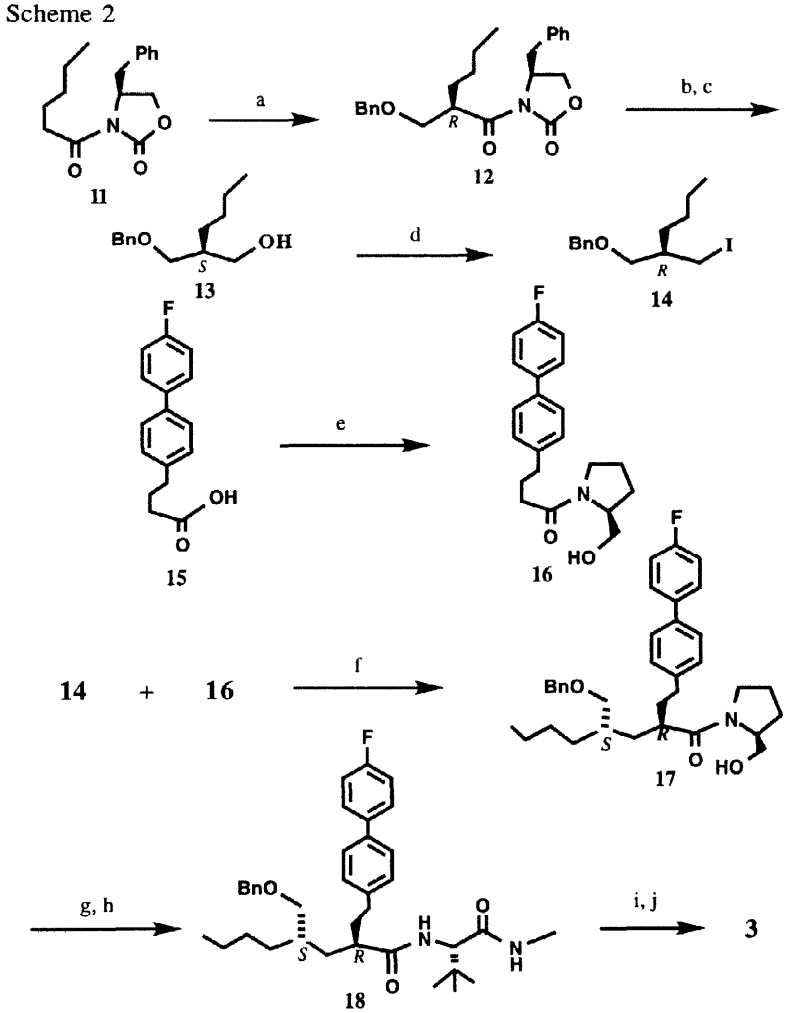


Reagents and conditions: (a) CH_2=(OMe)CH_3, PTS, CH_2Cl_2, 0 °C, 15 min, 95%; (b) $LiAlH_4$, THF, 2 h, 70%; (c) BnBr, KOtBu, THF, 88%; (d) 2 N HCl, THF, 2 h, rt, 100%; (e)[15] NIS, Ph_3P, 0 °C, 1 h, 77%; (f) L-prolinol, EDC, CH_2Cl_2, 75%; (g) LDA, DMPU, THF, -80 to -20 °C, 65%; (h) 2 N HCl, reflux, 30 h, 62%; (i) L-*tert*-Gly-NHPh, EDC, HOBt, 78%; (j) H_2, 20% $Pd(OH)_2$, MeOH, 40 psi, 15 h; (k) Jones' reagent, acetone, 0 °C, 0.5 h, 68% in last two steps.

The same methodology was applied to the synthesis of **3**, which has different P1 (*n*-butyl), P1' (4-fluorobiphenylethyl), and P3' (methyl) groups. Here we required the electrophile **14** and the chiral amide **16**, which were prepared as outlined in Scheme 2. The oxazolidinone amide **11** was prepared from hexanoyl chloride and (4*S*)-4-benzyl-2-oxazolidinone (with *n*-BuLi) in THF in 93% yield.[16] Trichlorotitanium enolate of **11** in CH_2Cl_2 was obtained by treatment of the amide successively with 1.05 equiv each of $TiCl_4$ and Et_3N. Subsequent treatment of this enolate with 1.6 equiv of chloromethyl benzyl ether provided **12** selectively in 90% yield.[13] Direct reduction of **12** with $LiAlH_4$ in THF or $LiBH_4$ in Et_2O[17]with 1.0 equiv of H_2O would provide the alcohol **13**. A two-step protocol as reported here gave **13** in 94% yield. Iodination with NIS and Ph_3P[15] afforded 2(*R*)-(benzyloxymethyl)hexyl iodide (**14**) in 74% yield. The chiral amide **16** was obtained from **15**[10] and L-prolinol as described before. Selective alkylation of the lithium enolate of **16** with the electrophile **14** again proceeded well (62% yield) to provide **17**. Acid

hydrolysis followed by amide coupling with L-*tert*-Gly-NHMe hydrochloride (NMM, EDC, HOBt in DMF) gave the intermediate **18**, which was hydrogenolyzed and oxidized to afford **3** in 30% overall yield in the last four steps. Here again we obtained an enantiomerically pure product, which was identical to **3** reported previously.[10] Previous synthesis[10] used the oxazolidinone chiral auxiliary of **15** to selectively introduce *tert*-butoxycarbonylethyl moiety at the 2 position and formed a dianion with LDA (after oxazolidinone deacylation) for alkylation with *n*-butyl iodide. This process again afforded a mixture of diastereomers and required separation by HPLC as their esters.

Scheme 2



Reagents and conditions: (a) $TiCl_4$, Et_3N, CH_2Cl_2, $BnOCH_2Cl$, 90%; (b) LiOOH, aq THF, 96%; (c) $LiAlH_4$, THF, 98%; (d)[15] NIS, PH_3P, DMF, rt, 2 h, 74%; (e) L-prolinol, EDC, CH_2Cl_2, 70%; (f) LDA, DMPU, THF, -80 to -20 °C, 62%; (g) 2 N HCl, aq THF, reflux 2 d, 60%; (h) L-*tert*-Gly-NHMe, EDC, HOBt, NMM, 74%; (i) H_2, 20% $Pd(OH)_2$, MeOH, 40 psi, 15 h, 82%; (j) Jones' reagent, acetone, 0 °C, 0.5 h, 83%.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on silica gel GF254 (Analtech) plates, and the spots were detected by a ceric sulfate (1%)-sulfuric acid (10%) spray. Flash column chromatography was conducted on silica gel 60 (70-230 mesh ASTM). ^{1}H NMR spectra were recorded for solutions in deuterated chloroform or methanol on a Varian XL400 pulsed Fourier transformed instrument, with tetramethylsilane as the internal standard. Mass spectra were determined on a LKB 9000 mass spectrometer. Analytical results for compounds followed by elemental symbols were within 0.4% of calculated values. Conventional processing consisted of drying organic solutions with anhydrous sodium sulfate or magnesium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

Benzyl 3-Iodo-2(*R*)-methylpropyl Ether (6):

The iodide **6** was prepared from methyl 3-hydroxy-2(*S*)-methylpropionate (**4**) in five steps in 45% overall yield (see Scheme 1): ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.8 Hz, CH_3), 1.78 (m, CH), 3.28-3.41 (2 m, 2 CH_2), 4.52 (s, $PhCH_2$), 7.29-7.38 (m, ArH).

L-Prolinol 4-(4-*n*-propylphenyl)butanamide (8):

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 5.58 g, 29.11 mmol) was added to a solution of 4-(4-*n*-propylphenyl)butanoic acid (**7**; 5.0 g, 24.24 mmol) and (*S*)-2-pyrrolidinemethanol (L-prolinol; 2.39 mL, 24.35 mmol) in CH_2Cl_2 (30 mL), and the reaction mixture was stirred at room temperature overnight. The solution was washed with 5 N NaOH, dil HCl, brine, dried, and evaporated to dryness. The crude product was purified by flash column chromatography (CH_2Cl_2-MeOH, 99:1; v/v) to give **8** (5.26 g, 75%): ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, CH_3CH_2), 2.30 (t, $ArCH_2$), 2.55 (t, CH_2CO), 2.66 (t, CH_3CH_2), 3.34-3.47 (m, NCH_2), 3.53-3.69 (2 m, CH_2OH), 4.18-4.25 (m, NCHC), 5.19 (2 d, *J* = 2.2 and 7.8 Hz, OH), 7.10 (br s, ArH).

L-Prolinol 5-Benzyloxy-4(*S*)-methyl-2(*R*)-[2-(4-*n*-propylphenyl)ethyl]pentanamide (9):

LDA (1.5 M soln in cyclohexane; 10.7 mL, 16.04 mmol) was added dropwise to a solution of **8** (2.21 g, 7.64 mmol) in dry THF (20 mL) under nitrogen, and the reaction mixture was stirred at room temperature for 15 min. DMPU (1.94 mL, 16.04 mmol) was added, and the solution was cooled to -82 °C. A solution of **6** (2.11 g, 7.64 mmol) in dry THF (5 mL) was added dropwise. The solution was gradually warmed to -40 °C and stirred at this temperature for 4 h and kept at -20 °C overnight. The reaction was quenched with aqueous NH_4Cl and partitioned between EtOAc and water. The organic layer was washed with brine, dried, and evaporated to dryness. The crude product was purified by flash column chromatography (hexanes-ethyl acetate, 50:50; v/v) to give **9** (2.18 g, 65%): ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, CH_3CH_2), 0.95 (d, *J* = 6.5 Hz, CH_3CH), 3.54-3.68 (2 m, CH_2OH), 4.18-4.25 (m, NCHC), 4.42 (s, $PhCH_2$), 5.30 (2 d, *J* = 2.2 and 7.7 Hz, OH), 7.06-7.10 (m, *n*-PrArH), 7.26-7.35 (m, ArH).

5-Benzyloxy-4(*S*)-methyl-2(*R*)-[2-(4-*n*-propylphenyl)ethyl]pentanoic Acid:

A solution of **9** (1.87 g, 4.27 mmol) in THF (2 mL) was added 2 N HCl (36 mL), and the mixture was heated under reflux with vigorous stirring for 34 h. The reaction was cooled to 0 °C, and 2 N NaOH (40 mL) was added. After 10 min at 0 °C, the solution was acidified with conc HCl to pH 3. The product was extracted with EtOAc (3 x), and the organic layer was dried and evaporated to a residue, which was purified by flash column chromatography (hexanes-ethyl acetate-acetic acid, 80:20:0.5; v/v) to give the title compound (0.984 g, 62%): ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, CH_3CH_2), 0.92 (d, J = 6.6 Hz, CH_3CH), 3.21-3.28 (m, $BnOCH_2$), 4.44 (s, $PhCH_2$), 7.06 (s, *n*-PrArH), 7.31-7.32 (m, ArH); MS *m*/*z* 351 (M + 1).

5-Benzyloxy-4(*S*)-methyl-2(*R*)-[2-(4-*n*-propylphenyl)ethyl]pentanoic Acid 1-[(*S*)-*tert*-Butylglycine phenylamide] Amide (10):

EDC (500 mg, 2.61 mmol) was added to a solution of the above acid (801 mg, 2.17 mmol), L-*tert*-Gly-NHPh (449 mg, 2.18 mmol), and 1-hydroxybenzotrizole hydrate (440 mg, 3.26 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature overnight. The solution was washed with dil HCl, brine, dried, and evaporated to a residue, which was purified by flash column chromatography (hexanes-ethyl acetate, 85:15 to 80:20; v/v) to give **10** (787 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, CH_3CH_2), 0.94 (d, J = 6.6 Hz, CH_3CH), 1.08 (s, *t*-Bu), 3.20-3.30 (m, $BnOCH_2$), 4.45 (s, $PhCH_2$), 4.57 (d, J = 9.2 Hz, CH*t*-Bu), 6.31 (d, J = 9.2 Hz, NH), 6.98-7.10, 7.22-7.34 and 7.49 (3 m, ArH), 8.33 (s, NH); MS *m*/*z* 464 (M - PhNH).

5-Hydroxy-4(*S*)-methyl-2(*R*)-[2-(4-*n*-propylphenyl)ethyl]pentanoic Acid 1-[(*S*)-*tert*-Butylglycine phenylamide] Amide:

A solution of **10** (565 mg, 1.01 mmol) in methanol (10 mL) was hydrogenated over 20% $Pd(OH)_2$ (113 mg) at 70 psi for 15 h. The catalyst was filtered off and washed with methanol. The combined filtrates were evaporated to a syrup (458 mg): ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.7 Hz, CH_3CH), 0.92 (t, J = 7.4 Hz, CH_3CH_2), 1.10 (s, *t*-Bu), 1.23-1.29 (m, $CHCH_2OH$), 1.60 (q, CH_3CH_2), 1.75-2.09 (3 m, $CH_2CH(CO)CH_2$), 2.45 (m, CHCO), 2.53 and 2.60 (2 t, 2 $ArCH_2$), 2.93, 3.25 and 3.56 (3 m, CH_2OH), 4.68 (d, J = 9.2 Hz, CH*t*-Bu), 6.73 (d, J = 9.2 Hz, NH), 7.02-7.09, 7.22-7.26 and 7.47-7.49 (3 m, ArH), 8.79 (s, NHPh); MS *m*/*z* 467 (M + 1). Anal. Calcd for $C_{29}H_{42}N_2O_3$: C, 74.64; H, 9.07; N 6.00. Found: C, 74.37; H, 9.14; N, 5.84.

4(*S*)-Methyl-2(*R*)-[2-(4-*n*-propylphenyl)ethyl]pentanedioic Acid 1-[(*S*)-*tert*-Butylglycine phenylamide] Amide (2):

Jones reagent (2.67 M; 0.586 mL, 1.57 mmol) was added dropwise to a stirred solution of the above alcohol (458 mg, 0.98 mmol) in acetone (50 mL) at 0-5 °C. After 0.5 h, 2-propanol was added to destroy excess oxidant. Water (50 mL) was added, and acetone was removed in vacuo. The product was extracted with EtOAc (3 x). The organic layer was washed with brine, dried, and evaporated to a residue, which was purified by flash column chromatography (hexanes-ethyl acetate-acetic acid, 70:30:0.5; v/v) to give **2** (333 mg, 68% overall yield in two steps): ^{1}H NMR ($CDCl_3$) δ 0.92 (t, CH_3CH_2), 1.12 (s, *t*-Bu), 1.13 (d, CH_3CH), 1.60 (q, CH_3CH_2), 2.52 (t, $CH_3CH_2CH_2$), 4.68 (d, J = 8.9 Hz, CH*t*-Bu), 6.88 (d, J = 8.9 Hz, NH), 7.00-7.08

(m ArH), 7.19 (t, ArH), 7.49 (d, ArH), 9.02 (s, NHPh); MS *m / z* 481 (M + 1). Anal. Calcd for $C_{29}H_{40}N_2O_4$: C, 72.47; H, 8.39; N, 5.83. Found: C, 72.62; H, 8.41; N, 5.69.

4(*S*)-Benzyl-3-(1-oxohexyl)-2-oxazolidinone (11):

n-Butyllithium (2 M soln in pentane; 77 mL, 153.8 mmol) was added dropwise to a stirred solution of 4(*S*)-benzyl-2-oxazolidinone (25 g, 141.1 mmol) in dry THF (250 mL) at -78 °C under nitrogen. Hexanoyl chloride (21 mL, 149.5 mmol) was added portionwise, and the mixture was kept at -78 °C for 1 h and warmed to 0 °C. Saturated aqueous $NaHCO_3$ (100 mL) was added, and the mixture was stirred at 0 °C for 0.5 h. The product was extracted with CH_2Cl_2 (3 x), and the combined organic extracts were washed with 5% Na_2CO_3 (100 mL), brine, dried, and evaporated to a syrup. The crude product was purified by flash column chromatography on silica gel (1 kg) with hexanes-ethyl acetate (97:3 to 90:10 to 85:15, v/v) as the eluant. The desired fractions were combined and evaporated to an oil (36.17 g, 93%): ^{1}H NMR ($CDCl_3$) δ 0.90-0.94 (m, CH_3), 1.35-1.39 (m, $CH_3CH_2CH_2$), 1.68-1.72 (m, $CH_3CH_2CH_2CH_2$), 2.77 (q, J = 9.6 and 13.3 Hz, $CHCH_2O$), 3.30 (q, J = 3.3 and 13.3 Hz, $CHCH_2O$), 2.93 (m, CH_2CO), 4.15-4.23 (m, $PhCH_2$), 4.64-4.70 (m, $CHCH_2Ph$), 7.21-7.36 (m, ArH); MS *m / z* 276 (M + 1). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N 5.09. Found: C, 69.93; H, 7.78; N, 5.09.

4(*S*)-Benzyl-3-[1-oxo-2(*R*)-(benzyloxymethyl)hexyl]-2-oxazolidinone (12):

A solution of **11** (16 g, 58.1 mmol) in dry CH_2Cl_2 (110 mL) was cooled to 0 °C, degassed, and kept under nitrogen. Titanium(IV) chloride (1 M soln in CH_2Cl_2; 61 mL, 61 mmol) was added portionwise to the vigorously stirred solution producing a bright yellow slution. After 5 min, triethylamine (8.5 mL, 61.3 mmol) was added dropwise giving a deep red homogeneous solution. This enolate solution was stirred at 0 °C for 1 h, after which benzyl chloromethyl ether (~80% pure; 20 mL, 115.5 mmol) was added slowly. The reaction mixture was stirred at this temperature for 3 h and at room temperature for 2 h over which time the dark red color faded to a pale yellow color. The reaction was quenched with saturated NH_4Cl (200 mL). The two layers were separated, and the aqueous layer was back extracted with CH_2Cl_2 (2 x). The combined organic extracts were washed with aqueous $NaHCO_3$, brine, dried, and evaporated to a yellow oil. The crude product was purified by flash column chromatography (hexanes-ethyl acetate, 90:10; v/v) to give crystalline **12** (20.7 g, 90%): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0 Hz, CH_3CH_2), 1.23-1.34 (m, $CH_3CH_2CH_2$), 1.52 and 1.70 (2 m, $CH_3CH_2CH_2CH_2$), 2.68 and 3.23 (2 q, $CHCH_2O$), 3.65 and 3.79 (2 q, $BnOCH_2$), 4.12 and 4.17 (2 q, $PhCH_2CH$), 4.24 (m, CHCO), 4.54 (q, $PhCH_2O$), 4.73 (m, $CHCH_2Ph$), 7.18-7.33 (m, ArH); MS *m / z* 396 (M + 1). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.93; H, 7.33; N, 3.55.

2(*R*)-(Benzyloxymethyl)hexanoic Acid:

A solution of **12** (12.4 g, 31.35 mmol) in THF (200 mL) and water (50 mL) was cooled to 0 °C. Hydrogen peroxide (30 wt%; 12.93 mL, 4 equiv) and lithium hydroxide monohydrate (2.64 g, 62.86 mmol) were added, and the reaction mixture was vigorously stirred at 0 °C for 1 h. A solution of sodium sulfite (17.38

g, 137. 94 mmol) in water (69 mL) and a solution of $NaHCO_3$ (13.16 g, 156.67 mmol) in water (230 mL) were added successively. The solution was basicified with NaOH to pH 10 and extracted with CH_2Cl_2 (3 x). The aqueous layer was acidified with HCl, and the product was extracted with EtOAc (3 x). The organic layer was dried and evaporated to an oil (7.08 g, 96%): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, CH_3CH_2), 1.29-1.33 (m, $CH_3CH_2CH_2$), 1.54 and 1.65 (2 m, $CH_3CH_2CH_2CH_2$), 2.72 (m, CHCO), 3.57 and 3.66 (2 q, $BnOCH_2$), 4.55 (s, $PhCH_2$), 7.26-7.35 (m, ArH); MS *m / z* 237 (M + 1).

2(*S*)-(Benzyloxymethyl)hexanol (13):

LDA (1 M soln in THF; 30 mL, 30 mmol) was added to the above acid (7.08 g, 29.96 mmol) in dry THF (150 mL), and the mixture was stirred at room temperature for 2 h. Water (1.14 mL), 15% NaOH (1.14 mL), and water (3.42 mL) were added dropwise successively. The solid was was filtered off and washed with THF, and the combined filtrates were evaoprated to dryness. The residue was partitioned between CH_2Cl_2 and water. The organic layer was separated and washed with brine, dried, and evaporated to give **13** as an oil (6.56 g, 98%): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, CH_3CH_2), 1.20-1.33 [m, $CH_3(CH_2)_3$, 1.88 (m, $CHCH_2O$), 2.63 (q, J = 4.4 and 7.0 Hz, OH), 3.46, 3.60-3.67 and 3.70-3.75 (3 m, 2 CH_2O), 4.52 (q, $PhCH_2$), 7.27-7.37 (m, ArH); MS *m / z* 223 (M + 1). Compound **13** can also be prepared directly from **12** by reduction with $LiAlH_4$ in THF or $LiBH_4$ in Et_2O.[17]

2(*R*)-(Benzyloxymethyl)hexyl Iodide (14):

N-Iodosuccinimide (10.62 g, 47.2 mmol) was added portionwise to a stirred solution of **13** (6.56 g, 29.5 mmol) and triphenylphosphine (12.38 g, 47.2 mmol) in DMF (100 mL) at 0-5 °C. The brown solution was stirred at room temperature for 2 h. Methanaol and *n*-butanol were added, and the solution was evaporated to a residue, which was partitioned between Et_2O and water. The aqueous layer was back extracted with Et_2O (3 x). The combined ethereal layer was washed with sodium bisulfite (2 x), brine, dried, and evaporated to a small volume. Triphenylphosphine oxide was filtered off, and the filtrate was evaporated to dryness. The crude product was purified by flash column chromatography (hexanes-ethyl acetate, 98.5:1.5 to 98:2 to 80:20; v/v) to give **14** (7.25 g, 74%): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, CH_3CH_2), 1.20-1.37 [m, $CH_3(CH_2)_3$], 3.29-3.35 (m, CH_2I), 3.42-3.45 (m, $BnOCH_2$), 4.52 (s, $PhCH_2$), 7.27-7.36(m, ArH). Anal. Calcd for $C_{14}H_{21}IO$: C, 50.61; H, 6.37; I, 38.20. Found: C, 50.89; H, 6.48; I, 38.00.

L-Prolinol 4-(4-fluorophenyl)phenylbutanamide (16):

This compound was prepared as described for **8**. The crude product was purified by flash column chromatography (hexanes-ethyl acetate, 50:50 to EtOAc; v/v) to give **16** in 70% yield: ^{1}H NMR ($CDCl_3$) δ 1.52-1.60 and 1.79-1.97 (2 m, $NCCH_2CH_2$), 2.00-2.07 (m, $ArCCH_2C$), 2.34 (t, CH_2CO), 2.73 (t, CH_2Ar), 3.37-3.49 (m, NCH_2), 3.53-3.70 (2 m, CH_2OH), 4.19-4.26 (m, NCHC), 5.14 (q, J = 2.3 and 7.7 Hz, OH), 7.09-7.54 (3 m, ArH); MS *m / z* 342 (M + 1). Anal. Calcd for $C_{21}H_{24}FNO_2$: C, 73.88; H, 7.09; N, 4.10; F, 5.56. Found: C, 74.02; H, 7.03; N, 3.87; F, 5.70.

L-Prolinol 5-Benzyloxy-4(*S*)-*n*-butyl-2(*R*)-[2-(4-fluorophenyl)phenylethyl]pentanamide (17):
This compound was prepared from **14** and **16** as described for **9** from **6** and **8**. The crude product was purified by flash column chromatography (hexanes-ethyl acetate, 60:40; v/v) to give **17** in 62% yield: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, CH_3), 1.24-1.28 [m, $CH_3(CH_2)_3$], 2.52-2.62 (m, CH_2Ar), 2.71-2.78 (m, CHCO), 3.52-3.69 (2 m, CH_2OH), 4.21 (m, NCHC), 4.38 (s, $PhCH_2$), 5.34 (q, J = 2.1 and 7.8 Hz, OH), 7.10-7.55 (3 m, ArH). Anal. Calcd for $C_{35}H_{44}FNO_3$: C, 77.03; H, 8.13; N, 2.57; F, 3.48. Found: C, 76.89; H, 8.12; N, 2.48; F, 3.13.

5-Benzyloxy-4(*S*)-*n*-butyl-2(*R*)-[2-(4-fluorophenyl)phenylethyl]pentanoic Acid:
The acid hydrolysis was carried out as described before to give the title compound in 57% yield: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, CH_3), 1.17-1.29 [m, $CH_3(CH_2)_3$], 1.33 (m, CCHC), 1.46-2.05 [4 m, $CH_2CH(CO)CH_2$)], 2.54-2.75 (m, CHCO and $ArCH_2$), 3.33 (m, $BnOCH_2$), 4.45 (s, $PhCH_2$), 7.08-7.53 (3 m, ArH). Anal. Calcd for $C_{30}H_{35}FO_3$: C, 77.89; H, 7.63; F, 4.11. Found: C, 77.61; H, 7.47; F, 3.91.

5-Benzyloxy-4(*S*)-*n*-butyl-2(*R*)-{2-(4-fluorophenyl)phenylethyl]pentanoic Acid 1-[(*S*)-*tert*-Butylglycine methylamide] Amide (18):
EDC (50 mg, 0.261 mmol) was added to a solution of the above acid (100 mg, 0.216 mmol), L-*tert*-Gly-NHMe hydrochloride (41 mg, 0.229 mmol), *N*-methylmorpholine (29 mL, 0.264 mmol), and 1-hydroxybenzotrizole hydrate (44 mg, 0.326 mmol) in DMF (3 mL), and the mixture was stirred at room temperature overnight. Ethyl ether and water were added, and the aqueous layer was back extracted with Et_2O (2 x). The combined ethereal extracts were washed with brine, dried, and evaporated to dryness. The crude product was purified by preparative TLC (hexanes-ethyl acetate, 60:40; v/v) to give **18** (94 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 0.86 (t, CH_3), 0.99 (s, *t*-Bu), 2.79 (d, J = 4.8 Hz, NCH_3), 3.31 (q, $BnOCH_2$), 4.24 (d, J = 9.2 Hz, NHCHCO), 4.45 (s, $PhCH_2$), 5.92 (br s, N*H*CH_3), 6.19 (d, N*H*CH), 7.08-7.52 (3 m, ArH).

5-Hydroxy-4(*S*)-*n*-butyl-2(*R*)-[2-(4-fluorophenyl)phenylethyl]pentanoic Acid 1-[(*S*)-*tert*-Butylglycine methylamide] Amide:
A solution of **18** (88 mg, 0.149 mmol) in methanol (3 mL) was hydrogenated over 20% $Pd(OH)_2$ (21 mg) at 40 psi for 6 h. The catalyst was filtered off and washed with methanol. The combined filtrates were evaporated to a residue, which was purified by preparative TLC (hexanes-ethyl acetate, 60:40; v/v) to give the alcohol (61 mg, 82%): MS m/z 499 (M + 1).

4(*S*)-*n*-Butyl-2(*R*)-[2-(4-fluorophenyl)phenylethyl]pentanedioic Acid 1-[(*S*)-*tert*-Butylglycine methylamide] Amide (3):
The Jones oxidation was carried out as described for **2**. The crude product was purified by flash column chromatography (hexanes-ethyl acetate-acetic acid, 60:40:0.5; v/v) to give **3** (46.5 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 0.88 (t, CH_3), 1.04 (s, *t*-Bu), 1.25-1.30 [m, $CH_3(CH_2)_3$], 2.78 (d, J = 4.7 Hz, NCH_3), 4.48 (d, J =

9.5 Hz, NHC*H*CO), 6.75 (br s, N*H*CH_3), 7.01-7.42 (3 m, ArH), 7.79 (d, N*H*CH); **MS** *m*/*z* 513 (M + 1). This compound was identical to **3** reported previously.[10]

REFERENCES

(1) Woessner, J. F. *FASEB J.* **1991**, *5*, 2145.

(2) Walakovits, L. A.; Bhardwaj, N.; Gallick, G. S.; Lark, M. W. *Arthritis Rheum.* **1992**, *35*, 35.

(3) Gravallese, E. M.; Darling, J. M.; Ladd, A. L.; Katz, J. N.; Glimcher, L. H. *Arthritis Rheum.* **1991**, *34*, 1076.

(4) Okada, Y.; Shinmei, M.; Tanaka, O.; Naka, K.; Kimura, A.; Nakanishi, I.; Bayliss, M. T.; Iwata, K.; Nagase, H. *Lab. Invest.* **1992**, *66*, 680.

(5) Chapman, K. T.; Kopka, I. E.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Izquierdo-Martin, M.; Niedzwiecki, L.; Chang, B.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Hagmann, W. K. *J. Med. Chem.* **1993**, *36*, 4293.

(6) Sahoo, S. P.; Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Esser, C. K.; Kopka, I. E.; Polo, S. A.; Sperow, K. M.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Stein, R. L.; MacCoss, M.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2441.

(7) Esser, C. K.; Kopka, I. E.; Durette, P. L.; Harrison, R. K.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Stein, R. L.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 539.

(8) Chapman, K. T.; Wales, J.; Sahoo, S. P.; Niedzwiecki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Stein, R. L.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 329.

(9) Chapman, K. T.; Durette, P. L; Caldwell, C. G.; Sperow, K. M.; Niedzwiecki, L. M.; Harrison, R. K.; Saphos, C.; Christen, J. M.; Olszewski, J. M.; Moore, V. L.; MacCoss, M.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 803.

(10) Esser, C. K.; Bugianesi, R. L.; Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Girotra, N. N.; Kopka, I. E.; Lanza, T. J.; Levorse, D. A.; MacCoss, M.; Owens, K. A.; Ponpipom, M. M.; Simeone, J. P.; Harrison, R. K.; Niedzwiecki, L.; Becker, J. W.; Marcy, A. I.; Axel, M. G.; Christen, A. J.; McDonnell, J.; Moore, V. L.; Olszewski, J. M.; Saphos, C.; Visco, D. M.; Shen, F.; Colletti, A.; Krieter, P. A.; Hagmann, W. K. *J. Med. Chem.* **1997**, *40*, 1026.

(11) The corresponding bromide prepared from (*S*)-3-hydoxyisobutyric acid was reported by Branca, Q.; Fishchli, A. *Helv. Chim. Acta* **1977**, *60*, 925.

(12) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.

(13) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(14) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.

(15) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohyd. Res.* **1972**, *24*, 45.

(16) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, Jr. J. F. *Tetrahedron* **1988**, *44*, 5525.

(17) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.