*Tetrahedron* Vol. 47, No. 16/17, pp. 2785-2800, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00


# SYNTHESIS OF RENIN INHIBITORS POSSESSING HYDROXYETHYLENE ISOSTERE RESIDUE FROM 3,4,6-TRI-O-ACETYL-D-GLUCAL VIA LACTONE PRECURSOR

Masao Shiozaki* and Yoshiyuki Kobayashi

New Lead Research Laboratories, Sankyo Co. Ltd.
Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan

Tadashi Hata and Youji Furukawa

Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd.
Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan

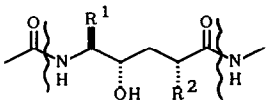
(*Received in Japan* 13 *November* 1990)

Abstract: Syntheses of precursors for renin inhibitors possessing hydroxyethylene isostere residue from 2,4,6-tri-O-acetyl-D-glucal via lactone precursor is described. This route makes it possible to synthesize analogues with various substituents at C-2 and C-5 of the hydroxyethylene isostere residue.

In recent years, there has been a growing interest in the use of enzyme inhibitors as therapeutic agents. It is claimed that inhibitors of the enzymes for conversion from angiotensin I to II are effective for the medical treatment of the high blood pressure. And also the inhibitors of aspartyl proteases (for example: renin) are effective for reducing the high blood pressure. To date, many statine and hydroxyethylene dipeptide isostere derivatives have been reported as aspartyl protease inhibitors.[1] In addition, in most recent years, the studies for these compounds have been spurred increasingly, because it was found that these analogues were effective as one of powerful inhibitors for an aspartic-type protease of human immunodeficiency virus (HIV).[2]

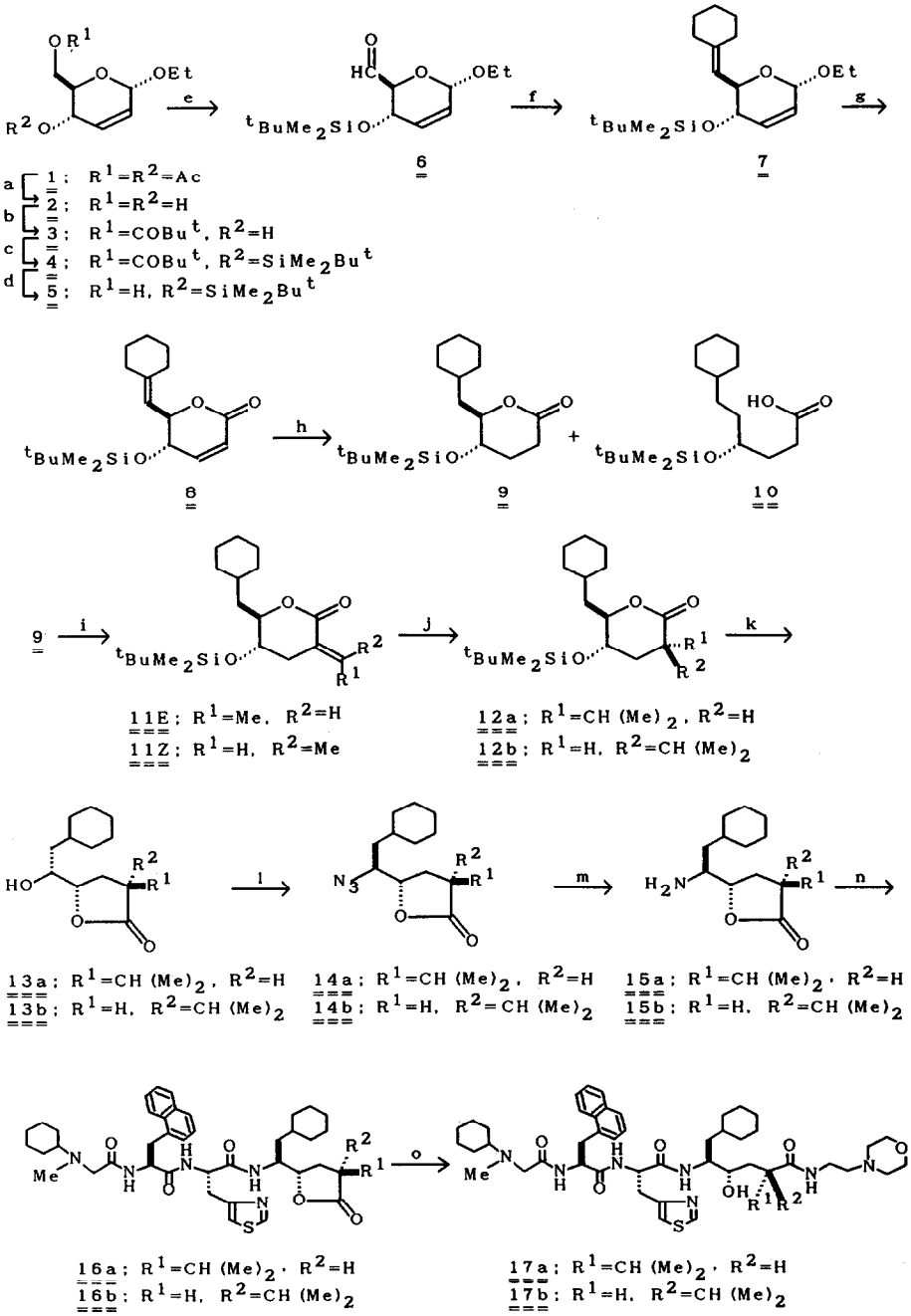
It has been studied that the replacement of peptide bonds by isosteres (statine or hydroxyethylene dipeptide) imparts greater activity, selectivity and stability to peptides with interesting pharmacological properties.[3] The hydroxyethylene dipeptide isostere is a homologue of statine (the unusual amino acid found in the naturally occurring pepstatin).[4] Peptides containing the (2S,4S,5S) hydroxyethylene dipeptide isosters (in this case, C-2 = isopropyl) with this chirality are potential inhibitors of renin.[1,3]

We describe here in detail an alternative and improved synthesis of a renin inhibitor with this (2S,4S,5S) isostere unit (17a) and its C-2 epimer



Hydroxyethylene dipeptide isostere residue

Scheme 1



(a) cat. KOH/EtOH, rt, 16 h, quantitatively; (b) pivaloyl chloride, pyridine-DMAP, rt, 16 h, THF, 85%; (c) t-$BuMe_2SiCl$, DMAP, $CH_2Cl_2$, reflux, 3 h, 98%; (d) $LiAlH_4$, THF, 5°C, 15 min, 84%; (e) PCC, MS-3A, $CH_2Cl_2$, rt, 2 h, 56%; or DCC, DMSO, cat. $H_3PO_4$, rt, 16 h, 57%; (f) $Ph_3P(C_6H_{11})Br$, $LiN(TMS)_2$, THF, reflux, 45 min, 67%; (g) Jones reagent, acetone, 0-5°C, 10 min, 57%; (h) $H_2$, 5% Pd/C, EtOAc, rt, 86%; (i) 1. MeCHO, $LiN(TMS)_2$, THF, -78°C, 15 min: 2. $MeSO_2Cl$, pyridine, rt, 1 h: 3. DBN, THF, rt, 10 min, overall E=78% and Z=4%; (j) $Me_2CuLi$, $Et_2O$, 0-5°C, 15 min, a=49% and b=49%; (k) MeOH:dil HCl (conc. HCl:$H_2O$=1:3)=6:1, reflux, 20 min, a=100% and b=94%; (l) DEAD, $Ph_3P$, $(PhO)_2P(O)N_3$, THF, 24°C, 1 h; (m) $H_2$, 10% Pd/C, EtOAc, rt, two steps a=87% and b=95%; (n) (N-cyclohexyl-N-methyl)glycyl-[3-(1-naphthyl)]-L-alanyl-[3-(4-thiazolyl)]-L-alanine, $(EtO)_2P(O)CN$, $Et_3N$, THF, 24°C, 1 h, a=60% and b=56%; (o) 4-(2-aminoethyl)morpholine, 80°C, 10 h, a=69% and b=72%.

(17b) for comparison of inhibition activity via their lactone form, 15a[5] and 15b, from 3,4,6-tri-O-acetyl-D-glucal. The approach involves a novel route to 15a and 15b, and allows for wide variation of two side chains at both C-2 and C-5 positions. Syntheses of the hydroxyethylene dipeptide isostere unit were reported by several groups.[6] However, in these syntheses, the production of diastereomers at more than two chiral centers was inevitable. We could reduce the positions, which might result to produce 8 diastereomers at three chiral centers, to one position by use of sugar as a starting material.

3,4,6-Tri-O-acetyl-D-glucal was converted to ethyl 4-O-tert-butyldimethylsilyl-2,3-dideoxy-α-D-erythro-hex-2-enodialdopyranoside-(1,5) 6 by a modified method of Valverde et al.[7] Compound 1[8] obtained from 3,4,6-tri-O-acetyl-D-glucal was treated with catalytic amount of KOH in EtOH to give diol 2. The compound 2 was treated with pivaloyl chloride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) to give 6-pivaloyloxy compound 3, which was further converted to 4-silyl compound 4 by treatment with t-butyldimethylsilyl chloride and $Et_3N$. Deprotection of 4 with $LiAlH_4$ in THF gave compound 5. Treatment of 5 with 1,3-dicyclohexylcarbodiimide (DCC)-dimethyl sulfoxide (DMSO) containing a catalytic amount of $H_3PO_4$ gave an aldehyde 6.

Wittig reaction of 6 with two equivalents of cyclohexyltriphenylphosphorane in THF at room temperature for 1.5 h gave 7 (67% yield) as a fragrant gum. Treatment of 7 in acetone with Jones reagent at 0°C for 10 min gave 8 (57% yield) as a fragrant solid, mp 58-59°C, $[\alpha]_D^{24}$+109.7° (c=1.9, $CHCl_3$). Hydrogenation of 8 in EtOAc at room temperature under 1 atm. by use of 5% Pd on carbon as a catalyst gave 9 (86% yield) and a hydrolyzed product 10.[9] In the next isopropylation, it is easily predicted that isopropylation of an activated methylene anion by an ester carbonyl

except for the doubly activated methine anion by another activating group is extremely difficult. In fact, the usual direct isopropylation of the carbanion of 9 with isopropyl iodide failed to give 12. So, treatment of 9 in THF with $LiN(SiMe_3)_2$ and MeCHO at -78°C gave a mixture of diastereomers of hydroxyethyl compounds which were mesylated with mesyl chloride (MsCl) in pyridine at room temperature to give a mixture of diastereomers, and the mesylated compounds were demesylated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in THF at room temperature to give an E:Z (88:5) mixture of exo-α,β-unsaturated lactone 11E and its endo-isomer 11Z in 93% yeild, and finally methylated with $Me_2CuLi$ to give a 1:1 mixture of diastereomers 12a and 12b (81% yield from 4). It was difficult to separate this mixture on a short silica gel column, because of the close $R_f$ value of each isomer (12a: $R_f$=0.393; 12b: $R_f$=0.533; cyclohexane:EtOAc= 9:1). However, use of silica gel more than 300 weight times of this mixture made it possible to separate 12b as a pure solid (mp 45-47°C) from the mixture. On the other hand, fortunately fractional recrystallization of the mixture 12a and 12b in cold methanol gave 12a as a solid (mp 91-92°C), and (2R)-isomer 12b was remaining in mother liquor. The mixture rich in 12b was equilibrated by the use of 1.1 equiv of $LiN(SiMe_3)_2$ at -78°C for 5 min to give a 1:1 mixture of 12a and 12b in quantitative yield. Thus, the undesired stereoisomer 12b was converted to 12a in good yield by repeating this procedure. On the other hand, equilibration of 12a, 12b, or a mixture of 12a and 12b with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 140°C for 1 h gave a 1:3 mixture of 12a and 12b in 99% yield. In this stage, we could not determine the configuration of isopropyl group. However, in latter stage, we could correlate the configurations of 12a and 12b to those of 15a and 15b.

Treatment of 12a in MeOH-4N HCl (5:1) at reflux temperature for 20 min gave 13a (94% yield) as a solid (mp 88-90°C). Mitsunobu reaction of 13a with diethyl azodicarboxylate (DEAD)-triphenyl phosphine for 5 min and then diphenylphosphoryl azide in THF at room temperature for 1.5 h gave an azide 14a (90% yield) as an oil with the complete inversion of configuration.[10] Compound 14a was hydrogenated in EtOAc by use of 10% Pd-C as a catalyst to give an amine 15a[5,11,14] (96% yield, mp 48-49°C).

The lactone amine 15a was further converted to one of renin inhibitors possessing the hydroxyethylene dipeptide isosteres 17a as follows. The reaction of 15a in THF with (N-cyclohexyl-N-methyl)glycyl-[3-(1-naphthyl)]-L-alanyl-[3-(4-thiazolyl)]-L-alanine[12] by use of diethyl cyanophosphonate-$Et_3N$ as a condensing agent gave triamide lactone 16a (72% yield from 13a) as a gum. The lactone 16a in 4-(2-aminoethyl)morpholine was allowed to stand for 10 h at 80°C to yield 17a (72% yield) as a gum. And also, compound 12b was converted to 17b via lactone amine 15b in 38% overall yield according to the same procedure as conversion of 12a to 17a.

The stereochemistry of 15b was confirmed as its benzoyl derivative 18 (mp, 202-203°C) by X-ray crystallographic analysis. (Figure 1).

Thus this synthetic methodology of aminolactone 15a should provide a versatile way for wide variation of side chains at C-2 and C-5, especially C-2 isopropyl group which is difficult to introduce, as well as independent control of stereochemistry at each of the three asymmetric centers. And it is obvious that this synthetic method for compounds 17a and 17b via 15a and 15b is also applicable for the synthesis of the HIV protease inhibitors possessing hydroxyethylene dipeptide isostere.

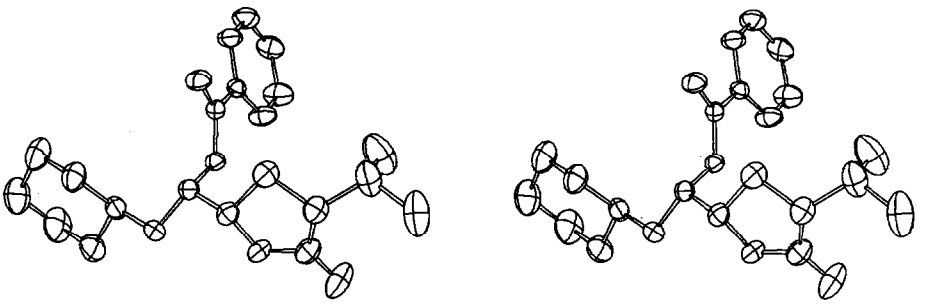


Figure 1. Stereoview of the crystal structure of compound 18.

The inhibitory potency against human renin of 17a was $IC_{50}$=3.5 x $10^{-8}$M, however that of isopropyl epimer 17b was 3.2 x $10^{-7}$M using sheep angiotensinogen as a substrate. This value of 17a for renin inhibition was strong in vitro evaluation, however in vivo test, the oral absorption (marmosets) was very low, and 17a did not show a clear antihypertensive effect.

Acknowledgement: We thank Dr. Yasuteru Iijima for measuring renin inhibition activity.

## EXPERIMENTAL

All melting points (mp) were uncorrected. $^1$H NMR spectra were recorded at 60 MHz and 270 MHz using tetramethylsilane as an internal standard. Preparative TLC was performed on silica gel plates (Merck 60 $PF_{245}$), and column chromatography was carried out on columns packed with Merck silica gel 60 using slightly increased pressure (1.4 atm.) for elution.

Ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (2).

A suspension of 1 (45.6 g, 185 mmol) in 99.5% EtOH (600 mL) containing KOH (200 mg) was allowed to stand overnight at room temperature. The suspension became a clear solution. The solution was concentrated in vacuo to give an oil, which was dissolved in benzene (500 mL), and again concentrated in vacuo to give 32.2 g of 2 as a solid, quantitatively. This was employed for the next reaction without purification. Mp 63-66°C. IR $\nu_{max}$(Nujol) 3390, 3270 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$ + $D_2O$) δ 1.24 (3H, t, J=7.0 Hz), 3.46-3.98 (6H, m, C4-H, C5-H, C6-$H_2$, $OCH_2Me$), 4.80-4.84 (1H, m, C1-H), 6.32-6.37 (2H, m, C2-H, C3-H). Anal. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.10; H, 8.15.

Ethyl 2,3-dideoxy-6-O-pivaloyl-α-D-erythro-hex-2-enopyranoside (3).

To a solution of diol 2 (30.0 g, 172 mmol) in THF (800 mL), pivaloyl chloride (31.2 g, 259 mmol), pyridine (27.3 g, 345 mmol) and DMAP (2.1 g, 17 mmol) was added, and the mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with EtOAc (1.5 L), washed with dil. HCl, $H_2O$, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give an oil which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (2:1) gave 37.8 g of 3 (85%). IR $\nu_{max}$(neat) 3460, 1728 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 1.24 (9H, s), 1.24 (3H, t, J=7.0 Hz), 2.23 (1H, d, J=6.8 Hz, exchanged with $D_2O$, C4-OH), 3.56 (1H, m, C5-H), 3.80-3.91 (2H, m, C1-$OCH_2Me$), 4.00 (1H, m C4-H), 4.29 (1H, dd, J=2.4, 12.2 Hz, C6-H), 4.45 (1H, dd, J=5.4, 12.2 Hz, C6-H), 4.99 (1H, d, J=1.0 Hz, C1-H), 5.76 (1H, dt, J=10.3, 2.5 Hz, C3-H), 5.96 (1H, dd, J=10.2, 1.0 Hz, C2-H). Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.00; H, 8.48.

Ethyl 4-O-(tert-butyldimethylsilyl)-2,3-dideoxy-6-O-pivaloyl-α-D-erythro-hex-2-enopyranoside (4).

To a solution of 3 (32.4 g, 125 mmol) in $CH_2Cl_2$ (150 mL) was added t-$BuMe_2SiCl$ (22.6 g, 150 mmol) and DMAP (18.4 g, 150 mmol). The reaction mixture was refluxed for 3 h, diluted with EtOAc, washed with dil. HCl, $H_2O$, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give 46.0 g of 4 (98%) as an oil, which was employed for the next reaction without further purification. Analytical sample was chromatographed on a silica gel column. IR $\nu_{max}$(neat) 1733 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.21 (9H, s), 1.21 (3H, t, J=7.5 Hz), 3.3-4.6 (6H, m, C4-H, C5-H, C6-$H_2$, C1-$OCH_2$), 4.93 (1H, m, C1-H), 5.65 (1H, m, C2-H), 5.87 (1H, d, J=11 Hz, C3-H). MS m/z 315 ($M^+$-Bu), 263. Anal. Calc. for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74. Found: C, 60.93; H, 9.66.

Ethyl 4-O-(tert-butyldimethylsilyl)-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (5).

To a solution of 4 (10.0 g, 26.8 mmol) in THF (100 mL) was added $LiAlH_4$ (1.2 g, 31.6 mmol) at 5°C with stirring. After 15 min, the reaction mixture was quenched with AcOH, diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated to give 6.48 g of 5 (84%) as an oil, which was employed for the next reaction without further purification. Analytical sample was chromatographed on a silica gel column. IR $\nu_{max}$(neat) 3500 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 1.22 (3H, t, J=7 Hz), 1.97 (1H, m, exchanged with $D_2O$, OH) 3.2-4.4 (6H, m, C4-H, C5-H, C6-$H_2$, C1-$OCH_2$), 4.96 (1H, t-like, J=1 Hz, C1-H), 5.5-6.0 (2H, m, C2-H, C3-H). MS m/z 243 ($M^+$-OEt), 231 ($M^+$-Bu), 228. Anal. Calc. for $C_{14}H_{28}O_4Si$ (288.46): C, 58.29; H, 9.78. Found: C, 57.94; H, 9.41.

Ethyl 4-O-(tert-butyldimethylsilyl)-2,3-dideoxy-α-D-erythro-hex-2-enodialdopyranoside-(1,5) (6).

(a) Pyridinium chlorochromate (PCC) (6.45 g, 29.9 mmol) was dissolved in anhydrous $CH_2Cl_2$ (50 mL) and molecular sieves 3A (MS-3A) (10 g) were added to this solution. After stirring for 1.5 h, a solution of 5 (2.5 g, 8.67 mmol) in $CH_2Cl_2$ (5 mL) was added to this suspension. After 2 h with vigorous stirring at room temperature, the reaction mixture was filtered through a celite layer. The layer was washed with a small portion of $CH_2Cl_2$. The combined filtrate was passed through a silica gel column, and then elution with cyclohexane-EtOAc (4:1) gave 1.30 g of 6 (56%) as an oil. IR $\nu_{max}$(neat) 3600-3200 (hydrate), 1745 (aldehyde) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.11 (3H, s), 0.88 (9H, s), 1.22 (3H, t, J=7 Hz), 3.3-4.1 (3H, m, C4-H, C1-$OCH_2$), 4.28 (1H, m, C5-H), 5.02 (1H, m, C1-H), 5.7-5.85 (2H, m, C2-H, C3-H), 9.80 (1H, s, C6-H). Anal. Calc. for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.53; H, 9.38.

(b) To a solution of 5 (235 mg, 0.81 mmol) in DMSO (4 mL) was added DCC (520 mg, 2.52 mmol) and $H_3PO_4$ (60 mg, 0.61 mmol). The mixture was stirred for 16 h at room temperature. The precipitate was filtered, and washed with a small amount of EtOAc. The filtrate was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a mixture, which was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 133 mg of 6 (57%), which was identical with that obtained in the above (a).

Ethyl 4-O-tert-butyldimethylsilyl-6-cyclohexylidene-2,3,6-trideoxy-α-D-erythro-hex-2-enoaldopyranoside-(1,5) (7).

To a suspension of triphenylcyclohexylphosphonium bromide[13] (17.0 g, 40.0 mmol) in THF (100 mL) was added a solution of lithium

bis(trimethylsilyl)amide which was prepared from 1,1,1,3,3,3-hexamethyldisilazane (6.4 g, 40.0 mmol) in THF (30 mL) and n-BuLi (24.8 mL, 1.6 M in hexane, 40.0 mmol). The mixture was refluxed for 45 min to generate a deep red solution of triphenylcyclohexylphosphorane. This solution was cooled to 5°C, and to this solution was added a solution of 6 (5.68 g, 19.8 mmol) in THF (30 mL) under nitrogen. The mixture was stirred for 1.5 h at room temperature. The reaction mixture was filtered. The filtrate was concentrated *in vacuo* to give a residual mixture, which was dissolved in a small portion of $CH_2Cl_2$ and charged on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 4.68 g of 7 (67%) as an oil, which has a sweet smell. IR $\nu_{max}$(neat) 2930, 2860 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.21 (3H, t, J=7 Hz), 1.4-1.75 (6H, m), 1.9-2.4 (4H, m), 3.3-4.1 (3H, m, C4-H, C1-$OCH_2$), 4.43 (1H, t, J=9 Hz, C4-H), 4.94 (1H, m, C1-H), 5.07 (1H, d, J=9 Hz, C6-H), 5.5-5.95 (2H, m, C2-H, C3-H). MS m/z 307 ($M^+$-OEt), 295 ($M^+$-Bu), 228, 143. Anal. Calc. for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 67.44; H, 10.07.

[5S-(5α,6β)]-5-[(tert-Butyldimethylsilyl)oxy]-6-(cyclohexylidenemethyl)-5,6-dihydro-2H-pyran-2-one (8).

Jones reagent (40 mL) was added to a suspension of 7 (4.94 g, 14.0 mmol) in acetone (300 mL) and $MgSO_4$ (10 g) with stirring at ice cooling temperature. After the addition of Jones reagent, the mixture was stirred for 10 min, and poured into ice cooling sat. $NaHCO_3$ (35 g) solution. The whole was concentrated *in vacuo* to remove acetone, and the residue extracted with EtOAc. The extract was washed with $H_2O$ and brine, dried over $MgSO_4$, concentrated, and chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 2.57 g of 8 (57%) as a fragrant solid; mp 58-59°C (from hexane). $[\alpha]_D^{25}$ +109.7° (c=1.86, $CHCl_3$). IR $\nu_{max}$(neat) 1733, 1670 (w) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.3-1.8 (6H, m), 1.9-2.4 (4H, m), 4.27 (1H, dm, 8.5, 2 Hz, C4-H), 4.94 (1H, t, J=8.5 Hz, C5-H), 5.15 (1H, dd, J=2, 8.5 Hz, C6-H), 5.90 (1H, dd, J=2, 10 Hz, C2-H), 6.71 (1H, dd, J=2, 10 Hz, C3-H). MS m/z 265 ($M^+$-Bu), 247, 228, 198, 183, 173. Anal. Calc. for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.87; H, 9.30.

[5S-(5α,6β)]-5-[(tert-Butyldimethylsilyl)oxy]tetrahydro-6-(cyclohexylmethyl)-2H-pyran-2-one (9) and (4R)-4-(tert-Butyldimethylsilyloxy)-6-cyclohexylhexanoic acid (10).

A solution of 8 (2.04 g, 6.32 mmol) in EtOAc (200 mL) containing 5% Pd on carbon (1 g) was hydrogenolyzed for 1 h at room temperature. The reaction mixture was filtered, concentrated, and chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (5:1) gave 1.78 g of 9

(86%) as a solid, and elution with cyclohexane-EtOAc (1:1) gave 0.20 g of 10 (9%) as an oil. Physical data of 9: mp 76-78°C (from hexane). $[\alpha]_D^{25}$ +86.8° (c=1.04, $CHCl_3$). IR $\nu_{max}$(Nujol) 1740 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 0.9-2.2 (15H, m), 2.4-3.0 (2H, m), 3.5-3.9 (1H, m, C4-H), 4.0-4.5 (1H, m, C5-H). Anal. Calc. for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 65.97; H, 10.71. Physical data of 10: IR $\nu_{max}$(neat) 3500-2500, 1715 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 0.9-2.0 (17H, m), 2.2-2.6 (2H, m), 3.69 (1H, m, C4-H), 7.40 (1H, broad, COOH). Anal. Calc. for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 65.68; H, 11.23.

[5S-(5α,6β),3(E)]-5-[(tert-Butyldimethylsilyl)oxy]tetrahydro-6-(cyclohexylmethyl)-3-ethylidene-2H-pyran-2-one (11E) and [5S-(5α,6β),3(Z)]-5-[(tert-Butyldimethylsilyl)oxy]tetrahydro-6-(cyclohexylmethyl)-3-ethylidene-2H-pyran-2-one (11Z).

(i) To a solution of 9 (2.14 g, 6.56 mmol) in THF (25 mL) was added a solution of $LiN(SiMe_3)_2$, which was prepared from $HN(SiMe_3)_2$ (2.12 g, 13.1 mmol) in THF (10 mL) and n-BuLi (1.6 M in hexane, 8.2 mL, 13.1 mmol), at -78°C with stirring under nitrogen, and then after 10 min, a solution of MeCHO (5 mL, 89.4 mmol) in THF (5 mL) was added to this mixture, and stirred for 15 min. The reaction mixture was quenched with a solution of AcOH (2 mL) in THF (4 mL), diluted with EtOAc, washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was passed through a silica gel column. Elution with cyclohexane-EtOAc (9:1) and then EtOAc gave a mixture of four diastereomers (2.69 g) as a semi-solid.

(ii) The above obtained mixture of alcohols (2.69 g, 7.26 mmol) was dissolved in pyridine (40 mL), and to this solution was added $MeSO_2Cl$ (1.5 g, 13.1 mmol) at room temperature with stirring. After 1 h, the reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with $H_2O$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude mixture of diastereomers (3.28 g).

(iii) The mixture of mesylates (3.28 g, 7.35 mmol) was dissolved THF (50 mL) containing DBN (2.0 g). After 10 min stirring at room temperature, the reaction mixture was diluted with EtOAc, which was washed with dil. HCl, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a mixture of E and Z-geometrical isomers as a crude solid. The mixture was chromatographed on a silica gel column. Elution with cyclohexane-EtOAc (9:1) gave 0.10 g of 11Z (4%) (Rf=0.543) as an oil and 1.80 g of 11E (78%) (Rf=0.386) as a crystalline solid. Physical data of 11Z: IR $\nu_{max}$(neat) 1723, 1638 $cm^{-1}$. MS m/z 353 ($M^+$=1), 352 ($M^+$), 337, 319, 295, 277, 265. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.7-2.0 (25H m, containing 9H singlet

at δ 0.90), 2.2 (3H, m), 2.3-2.8 (2H, m), 3.4-3.9 (1H, m), 3.9-4.3 (1H, m), 5.9-6.4 (1H, m). Anal. Calc. for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.35; H, 10.11. Physical data of **11E**: mp 68-69°C (from hexane). IR $\nu_{max}$(Nujol) 1718, 1643 $cm^{-1}$. MS m/z 353 ($M^+$+1), 352 ($M^+$), 337, 319, 295, 277, 265. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.7-1.9 (25H m, containing 9H singlet at δ 0.88, and 3H, dd, J=1, 7 Hz, at δ 1.78), 2.2-3.0 (2H, m), 3.5-3.9 (1H, m), 4.0-4.4 (1H, m), 6.9-7.4 (1H, m). Anal. Calc. for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.24; H, 10.38.

[3S-(3α,5α,6β)]-5-[(tert-Butyldimethylsilyl)oxy]tetrahydro-6-(cyclohexylmethyl)-3-isopropyl-2H-pyran-2-one (**12a**) and [3R-(3α,5β,6α)]-5-[(tert-Butyldimethylsilyl)oxy]tetrahydro-6-(cyclohexylmethyl)-3-isopropyl-2H-pyran-2-one (**12b**).

To a suspension of CuI (602 mg, 3.17 mmol) in $Et_2O$ (6 mL) was added a solution of MeLi (1.5 M in $Et_2O$, 4.2 mL, 6.34 mmol) at 0°C under nitrogen with stirring to generate a solution of $LiCuMe_2$. To this solution was added a solution of **11E** (222 mg, 0.634 mmol, or **11Z**) in $Et_2O$ (5 mL). After 15 min, the reaction mixture was quenched with AcOH (0.5 mL), diluted with EtOAc, washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, concentrated in vacuo to give a mixture of two isomers. A short column chromatography of this crude mixture gave a 1:1 mixture of **12b** and **12a**. However this mixture was separable on a silica gel (100 g) column. Elution with cyclohexane-EtOAc (19:1) gave 113 mg of **12b** (49%), and 115 mg of **12a** (49%). The Rf values of **12b** and **12a** (cyclohexane:EtOAc=9:1) were 0.533 and 0.393, respectively. The 1:1 mixture was conducted to fractional crystallization. The 1:1 mixture (210 mg) was dissolved in MeOH (4 mL), and stored in a refrigerator to give 52 mg of soild. This was repeated once more in MeOH (0.3 mL) to give pure **12a** (43 mg). The **12b** rich mother liquor was concentrated, and equilibrated with a solution of $LiN(SiMe_3)_2$ (1.1 equivalents) in THF at -78°C to generate a 1:1 mixture of **12a** and **12b**, quantitatively. Physical data of **12a**: mp 91-92°C (needles from MeOH). $[\alpha]_D^{25}$ +68.7° (c=1.03, $CHCl_3$). IR $\nu_{max}$(Nujol) 1730 $cm^{-1}$. MS m/z 369 ($M^+$+1), 368 ($M^+$), 367, 353, 335, 311 ($M^+$-Bu), 293, 281, 225, 219. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.87 (9H, s), 0.94 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 1.0-2.1 (15H, m), 2.1-2.8 (2H, m), 3.4-4.3 (2H, m). Anal. Calc. for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94. Found: C, 68.65; H, 10.87. Physical data of **12b**: mp 45-47°C. $[\alpha]_D^{25}$ +93.9° (c=1.19, $CHCl_3$). IR $\nu_{max}$(Nujol) 1740 $cm^{-1}$. MS m/z 369 ($M^+$+1), 368 ($M^+$), 367, 353, 335, 311 ($M^+$-Bu), 293, 281, 225, 219. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.80-1.75 [27H, m, containing at δ 0.89, (9H, s), 0.95 (3H, d, J=6.6 Hz), 0.99 (3H, d, J=6.9 Hz)], 1.75-1.90 (3H, m, 1H + C3-$H_2$), 2.36 (1H, m, C2-$CHMe_2$), 2.62 (1H, m, C2-H),

3.76 (1H, q, J=5.1 Hz, C4-H), 4.19 (1H, dt, J=8.1, 5.1 Hz, C5-H). Anal. Calc. for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94. Found: C, 68.41; H, 10.93.

[3S-[3α,5β(S*)]]-5-(2-Cyclohexyl-1-hydroxyethyl)dihydro-3-isopropyl-2(3H)-furanone (13a).

A solution of 12a (395 mg, 1.07 mmol) in MeOH (30 mL) and dil. HCl (conc. HCl:$H_2O$=1:3, 5 mL) was refluxed for 20 min. The reaction mixture was concentrated in vacuo to give 274 mg of 13a (100%) as a solid; mp 88-90°C (needles from hexane). $[\alpha]_D^{25}$ +13.8° (c=1.3, $CHCl_3$). IR $\nu_{max}$(Nujol) 3450, 1732 $cm^{-1}$. MS m/z 254 ($M^+$), 212, 183, 128, 127, 109, 86. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.82-0.92 (1H, m), 0.95 (3H, d, J=6.8 Hz), 1.03 (3H, d, J=6.8 Hz), 1.13-1.30 (5H, m), 1.32-1.40 (1H, m), 1.40-1.55 (1H, m), 1.60-1.80 (5H, m), 6.8, 8.3, 13.2 Hz), 2.16 (1H, m), 2.29 (1H, ddd, J=5.4, 10.3, 13.2 Hz), 2.66 (1H, ddd, 5.4, 6.8, 10.7 Hz), 4.01 (1H, ddd, J=3.4, 6.8, 9.8 Hz), 4.32 (1H, ddd, J=3.4, 5.4, 8.3 Hz). Anal. Calc. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.66; H, 10.36.

[3R-[3α,5α(S*)]]-5-(2-Cyclohexyl-1-hydroxyethyl)dihydro-3-isopropyl-2(3H)-furanone (13b).

Compound 12b was treated as described above to give 13b in 94% yield; mp 78-79°C (needles from hexane). $[\alpha]_D^{25}$ +37.4° (c=1.0, $CHCl_3$). IR $\nu_{max}$(Nujol) 3480, 1761 $cm^{-1}$. MS m/z 254 ($M^+$), 212, 183, 128, 127, 109, 86. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.8-1.8 (19H, m, containing 3H, d, J=7.0 Hz, at δ 0.94 and 3H, d, J=7 Hz, at δ 1.05), 1.82 (1H, bs, OH), 1.97-2.13 (2H, m), 2.20 (1H, m), 2.60 (1H, ddd, J=5.1, 9.9, 11.7 Hz), 4.10 (1H, m, changed to a dt, J=9.5, 3.3 Hz, on addition of $D_2O$), 4.25 (1H, ddd, J=3.3, 6.6, 9.9 Hz). Anal. Calc. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.55; H, 10.46.

[3S-[3α,5β(R*)]]-5-(2-Cyclohexyl-1-azidoethyl)dihydro-3-isopropyl-2(3H)-furanone (14a).

To a solution of 13a (120 mg, 0.472 mmol) in THF (4 mL) was added $Ph_3P$ (187 mg, 0.713 mmol) and a solution of diethyl azodicarboxylate (124 mg, 0.712 mmol) in THF (1 mL) at room temperature with stirring. After 5 min, to this mixture was added a solution of $(PhO)_2P(O)N_3$ (196 mg, 0.712 mmol) in THF (1 mL). The mixture was stirred for 1 h at room temperature, diluted with EtOAc, washed with dil. HCl, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, concentrated to give an oily mixture, which was chromatographed on a silica gel column. Elution with cyclohexane- EtOAc (6:1) gave 10 mg of [3S-[3α,5β(E)]]-5-(2-cyclohexylvinylene)dihydro-3-isopropyl-2(3H)-furanone (Rf=0.625, cyclohexane:EtOAc=4:1), and 119 mg of 14a (90%, Rf=0.583, cyclohexane:EtOAc=4:1) as an oil. Physical data of [3S-[3α,5β(E)]]-

5-(2-cyclohexylvinylene)dihydro-3-isopropyl-2(3H)-furanone: IR $\nu_{max}$(neat) 1765 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.8-1.3 (10H, m, containing 3H, d, J=7.0 Hz, at δ 0.95 and 3H, d, J=6.6 Hz, at δ 1.04), 1.58-1.85 (6H, m), 1.90-2.30 (4H, m), 2.55 (1H, m), 4.86 (1H, dq, 1.5, 6.6 Hz, C5-H), 5.41 (1H, ddd, J=1.5, 6.6, 15.4 Hz, cyclohexyl-CH=), 5.71 (1H, ddd, J=1.1, 6.6, 15.4 Hz, =CH-C5). Physical data of **14a**: IR $\nu_{max}$(neat) 2110, 1772 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.9-1.8 (19H, m, containing 3H, d, J=6.6 Hz, at δ 0.95 and 3H, d, J=6.7 Hz, at δ 1.03), 2.08-2.22 (3H, m, C3-$CHMe_2$, C4-$H_2$), 2.70 (1H, ddd, J=4.8, 7.3, 9.7 Hz, C3-H), 3.39 (1H, quintet, J=4.0-4.4 Hz, C6-H), 4.41 (1H, ddd, J=4.0, 5.9, 7.7 Hz, C5-H). Anal. Calc for $C_{15}H_{25}N_3O_2$: C, 64.49; H, 9.02; N, 15.04. Found: C, 64.58; H, 9.14; N, 14.88.

[3R-[3α,5α(R*)]]-5-(2-Cyclohexyl-1-azidoethyl)dihydro-3-isopropyl-2(3H)-furanone (**14b**).

Compound **13b** (200 mg, 0.786 mmol) was treated as described above to give 225 mg of **14b**, which is, however, contaminating a small amount of $(PhO)_2P(O)N_3$ and diethyl azodicarboxylate having the same Rf value (Rf=0.546, cyclohexane:EtOAc=4:1). This was employed for the next reaction without further purification. IR $\nu_{max}$(neat) 2110, 1773 $cm^{-1}$. MS m/z 281, 280 ($M^+$+1), 275, 252, 169, 127, 124. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.83-1.85 (19H, m, containing 3H, d, J=7.0 Hz, at δ 0.96 and 3H, d, J=6.6 Hz, at δ 1.06), 1.89 (1H, dt, J=10.3, 12.1 Hz, C4-H), 2.17 (1H, dq, J=9.2, 6.2 Hz, C4-H), 2.22 (1H, m, C3-$CHMe_2$), 2.61 (1H, ddd, J=5.1, 9.2, 12.5 Hz, C3-H), 3.36 (1H, quintet, J=5.1 Hz, C6-H), 4.31 (1H, ddd, J=5.1, 5.9, 10.3 Hz, C5-H). Anal. Calc. for $C_{15}H_{25}N_3O_2$: C, 64.49; H, 9.02; N, 15.04. Found: C, 65.14; H, 9.02; N, 13.44.

[3S-[3α,5β(R*)]]-5-(2-Cyclohexyl-1-aminoethyl)dihydro-3-isopropyl-2(3H)-furanone (**15a**).

A solution of **14a** (100 mg, 0.358 mmol) in EtOAc (8 mL) was hydrogenolyzed under hydrogen using 10% Pd on carbon (200 mg), which was chromatographed on a silicagel short column. Elution with EtOAc gave 88 mg of **15a** (97%) as a solid. The X-ray sample of **15a**[5,11,14] was recrystallized at -10°C from hexane. Mp 48-49°C. IR $\nu_{max}$(Nujol) 3360, 3230 (w), 1750, 1600 (w) $cm^{-1}$. MS m/z 254 ($M^+$+1), 156, 127, 126. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.76-1.80 (21H, m, containing 3H, d, J=6.6 Hz, at δ 0.95 and 3H, d, J=6.9 Hz, at δ 1.00, and 2H, broad, $NH_2$ at δ 1.46), 2.05 (1H, m, C4-H), 2.08 (1H, m, C4-CH), 2.17 (1H, m, C3-$CHMe_2$), 2.63 (1H, ddd, J=5.1, 6.6, 9.5 Hz, C3-H, C5-CH), 2.79 (1H, m), 4.20 (1H, dd, J=6.6, 13.6Hz, C5-H). Anal. Calc. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.23; H, 10.70; N, 5.49.

[3R-[3α,5α(R*)]]-5-(2-Cyclohexyl-1-aminoethyl)dihydro-3-isopropyl-2(3H)-furanone (15b).

The crude compound 14b (50 mg, 0.179 mmol) obtained from 13b was treated as described above to give 42 mg of 15b (two steps 95%). This was employed for the next reaction without further purification. This compound was characterized as its benzamide. Physical data of benzamide (18) of 15b: Mp 202-203°C (needles from hexane-EtOAc). IR $\nu_{max}$(Nujol) 3360, 1762, 1638, 1606 (w) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.07-2.9 (23H, m, containing 3H, d, J=7 Hz, at δ 0.76 and 3H, d, J=7 Hz, at δ 0.95), 4.2-4.8 (2H, m), 6.03 (1H, d, J=9 Hz, NH), 7.3-7.9 (5H, m). Anal. Calc. for $C_{22}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.20; H, 9.21; N, 4.01.

Crystal structure of 18.[14] Colorless needle crystals were grown by slow evaporation in a mixture of EtOAc-hexane and mounted on a fully automated Rigaku AFC-5 X-ray diffractometer using Cu-Kα radiation. The unit cell parameters were a=b=10.985(2) and c=30.501(8) Å in space group $P6_5$ (Z=6). Of the 1891 reflections measured with θ< 130° employing a 2θ/ scan, 1514 were independently observed at a level F>3σ(F). Three reflections measured every 100 reflections showed no significant variation in intensity. The size of the crystal used was 0.8 x 0.3 x 0.2 mm, but no correction carried out for absorption. The structure was solved by the direct method using MULTAN84[15] and refined by the block-diagonal least-squares method with anisotropic thermal parameters. The positions of hydrogen atoms were estimated using standard geometry and included in refinement with isotropic thermal parameter. Final refinement converged at R=0.058. All computer programs were supplied by Rigaku for PANAFACOM U-1400.

[3S-[3α,5β(R*)]]-5-[2-Cyclohexyl-1-(N-cyclohexyl-N-methyl)glycyl-3-(1-naphthyl)-L-alanyl-3-(4-thiazolyl)-L-alanyl)aminoethyl]dihydro-3-isopropyl-2(3H)-furanone (16a).

A solution of 15a (26 mg, 0.103 mmol), (N-cyclohexyl-N-methyl)glycyl-[3-(1-naphthyl)]-L-alanyl-[3-(4-thiazolyl)]-L-alanine (61 mg, 0.116 mmol), and $Et_3N$ (30 mg, 0.297 mmol) in THF (5 mL) was added $(EtO)_2P(O)CN$ (32 mg, 0.196 mmol). After stirring for 16 h at room temperature, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated to give a residue, which was chromatographed on a silica gel column. Elution with EtOAc gave 47 mg of 16a (60%). IR $\nu_{max}$($CHCl_3$) 3320, 1767, 1670 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.60-1.74 (29H, m, containing 3H, d, J=7.0 Hz, at δ 0.94 and 3H, d, J=6.6 Hz, at δ 1.03), 1.95 (3H, s), 1.97-2.19 (3H, m, C3-$CHMe_2$, C4-$H_2$), 2.72 (1H, quintet, J=5.4 Hz, C3-H), 2.88 (2H, s, $NCH_2CO$), 2.98 (1H, dd, J=4.1, 14.3 Hz), 3.45 (1H, dd, J=9.7, 14.5 Hz), 3.50 (1H, dd, J=5.3, 15.2 Hz), 3.83 (1H, dd, J=5.0, 14.3 Hz),

4.03-4.17 (2H, m), 4.41 (1H, ddd, J=2.6, 6.3, 8.6 Hz), 4.56 (1H, quintet, J=4.8 Hz), 4.77 (1H, dt, J=7.7, 4.6 Hz), 6.87-8.52 (12H, m, 3xNH, olefinic 9H). MS m/z 759, 758, 757 ($M^+$), 646, 502, 408. Anal. Calc. for $C_{43}H_{59}N_5O_5S$: C, 68.13; H, 7.84; N, 9.24; S, 4.23. Found: C, 68.25; H, 7.71; N, 9.18; S, 4.20.

[3R-[3α,5α(R*)]]-5-[2-Cyclohexyl-1-(N-cyclohexyl-N-methyl)glycyl-3-(1-naphthyl)-L-alanyl-3-(4-thiazolyl)-L-alanyl)aminoethyl]dihydro-3-isopropyl-2(3H)-furanone (16b).

The compound 15b (42 mg, 0.166 mmol) obtained from 14b was treated as described above to give 76 mg of 16b (56%) as a gum. IR $\nu_{max}(CHCl_3)$ 3320, 1768, 1670 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.7-1.9 (29H, m, containing 3H, d, J=7.0 Hz, at δ 0.92 and 3H, d, J=6.6 Hz, at δ 1.11), 1.98 (3H, s), 2.02-2.21 (3H, m), 2.44 (1H, m), 2.82-3.02 (3H, m), 3.42 (1H, dd, J=9.9, 14.3 Hz), 3.50 (1H, dd, J=5.1, 15.0 Hz), 3.82 (1H, dd, J=5.1, 14.6 Hz), 4.08-4.17 (2H, m), 4.34 (1H, m), 4.55 (1H, quintet, J=4.8 Hz), 4.78 (1H, dt, J=7.3, 4.8 Hz), 6.90 (1H, d, J=9.2 Hz, NH), 7.09 (1H, d, J=1.1 Hz), 7.37-7.40 (2H, m), 7.41-7.63 (2H, m), 7.77 (1H, dd, J=3.3, 6.2 Hz), 7.87 (1H, d, J=7.7 Hz), 7.99-8.23 (2H, m), 8.24 (1H, d, J=8.4 Hz), 8.53 (1H, d, J=2.2 Hz). MS m/z 759, 758, 757 ($M^+$), 646, 505,, 408, 350, 153, 141, 126, 112. High resolution MS of 757: Found; 757.41981. Calc for $C_{43}H_{59}N_5O_5S$; 757.42361. Anal. Calc. for $C_{43}H_{59}N_5O_5S$: C, 68.13; H, 7.84; N, 9.24; S, 4.23. Found: C, 68.04; H, 7.61; N, 9.37; S, 4.12.

[2S,4S,5S]-6-Cyclohexyl-5-[(N-cyclohexyl-N-methyl)glycyl-3-(1-naphthyl)-L-alanyl-3-(4-thiazolyl)-L-alanyl)amino]-4-hydroxy-2-isopropylhexanoyl-[2-(4-morpholino)ethyl]amide (17a).

A solution of 16a (32 mg, 0.042 mmol) in 4-(2-aminoethyl)morpholine (400 mg, 3.07 mmol) was heated at 80°C for 10 h. The reaction mixture was concentrated by a pump to give a residue, which was chromatographed on a silica gel plate. Development with $CH_2Cl_2$-MeOH (10:1) gave 26 mg of 17a (Rf=0.525) (69%) in the UV sensitive part. IR $\nu_{max}$(Nujol) 3270, 1638 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.6-2.2 (39H, m, containing 3H, d, J=6.6 Hz, at δ 0.92, 3H, d, J=6.6 Hz, at δ 0.98, and 3H, s, at δ 1.25), 2.45-2.72 (5H, m), 2.90-3.04 (3H, m), 3.32-3.94 (11H, m), 4.48 (1H, m, changed to dd on addition of $D_2O$), 4.77 (1H, dt, J=4.4, 7.3 Hz), 6.64 (1H, d, J=8.8 Hz, NH), 7.14 (1H, d, J=1.8 Hz), 7.4-8.3 (10H, m), 8.58 (1H, d, J=1.8 Hz). MS m/z 887 ($M^+$), 870, 869, 759, 758, 757, 756, 646, 630, 505, 350, 126. High resolution positive FAB MS of [M+1]: Found; 888.5435. Calc for $C_{49}H_{74}N_7O_6S$; 888.5422. Anal. Calc. for $C_{49}H_{73}N_7O_6S$: C, 66.26; H, 8.28; N, 11.04; S, 3.61. Found: C, 66.44; H, 8.44; N, 10.76; S, 3.42%).

[2R,4S,5S]-6-Cyclohexyl-5-[(N-cyclohexyl-N-methyl)glycyl-3-(1-naphthyl)-L-alanyl-3-(4-thiazolyl)-L-alanyl)amino]-4-hydroxy-2-isopropylhexanoyl-[2-(4-morpholino)ethyl]amide (17b).

The compound 16b (40 mg, 0.053 mmol) was treated as described above to give 36 mg of 17b (72%). IR $\nu_{max}$($CHCl_3$) 3340, 2860, 2930, 1665, 1510 $cm^{-1}$. $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.6-2.2 (39H, m, containing 3H, d, J=6.6 Hz, at δ 0.92 and 3H, d, at δ 0.99, and 3H, s, at δ 1.99), 2.5-2.6 (5H, m), 2.9-3.0 (3H, m), 3.35-3.94 (11H, m), 4.47 (1H, m, changed to dd on addition of $D_2O$), 4.79 (1H, dt, J=4.4, 8.2 Hz), 6.76 (1H, d, J=8.8 Hz, NH), 7.13 (1H, d, J=1.5 Hz), 7.4-8.3 (10H, m), 8.57 (1H, d, J=2.2 Hz). MS m/z 888 ($M^+$+1), 870, 787, 758, 647, 631, 505, 408, 350. Anal. Calc. for $C_{49}H_{73}N_7O_6S$: C, 66.26; H, 8.28; N, 11.04; S, 3.61. Found: C, 65.97; H, 8.23; N, 10.69; S, 3.56.

## References and Notes


1. (a) M. Szelke, D. M. Jones, B. Atrash, A. Hallett, and B. J. Leckie, Peptides, Structure and Function (V. J. Hruby and D. H. Rich, ed), Pierce Chemical Co., Rockford, ICl, 1983, p. 579. (b) B. J. Leckie, J. Grant, A. Hallett, M. Hughes, D. M. Jones, M. Szelke, and M. Tree, Scott. Med. J. 1984, 29, 125. (c) D. H. Rich, F. G. Salituro, and M. W. Holladay, Peptides, Structure and Function (V. J. Hruby and D. H. Rich, ed), Pierce Chemical Co., Rockford, ICl, 1983, p. 511.
2. (a) I. Katoh, T. Yasunaga, Y. Ikawa, and Y. Yoshinaka, Nature 1987, 329, 654. (b) S. Seelmeier, H. Schmidt, V. Turk, and K. von der Helm, Proc. Natl. Acad. Sci. USA 1988, 85, 6612.
3. Reviews: (a) A. F. Spatola, Chemistry and Biochemistry of Amino Acids, Peptides, and Protaines (B. Weinstein, ed), Marcel Dekker, New York, 1983, Vol. 7, p. 267. (b) D. Tourwe, Janssen Chim. Acta, 1985, 3, 3.
4. (a) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada, and T. Takeuchi, J. Antibiotics 1970, 23, 259. (b) T. Miyano, M. Tomiyasu, H. Iizuka, S. Tomisaka, T. Takita, T. Aoyagi, and H. Umezawa, ibid 1972, 25, 489. (c) H. Morishima, T. Takita, and H. Umezawa, ibid 1972, 25, 551. (d) Idem, ibid 1973, 26, 115.
5. M. Shiozaki, T. Hata, and Y. Furukawa, Tetrahedron Lett. 1989, 30, 3669.
6. (a) B. E. Evans, K. E. Rittle, C. F. Homnick, J. P. Springer, J. Hirshfield, and D. F. Veber, J. Org. Chem. 1985, 50, 4615. (b) A. H. Fray, R. L. Kaye, and E. F. Kleinman, ibid 1986, 51, 4828. (c) J. S. Bindra, R. L. Rosati, and E. F. Kleinman, Eur. Pat. Appl. EP 212903p A2, 4 Mar, 1987. (d) D. J. Kempf, J. Org. Chem. 1986, 51, 3921. (e) M. W. Holladay and D. H. Rich, Tetrahedron Lett. 1983, 24, 4401. (f) M. W.

Holladay, F. G. Salituro, and D. H. Rich, J. Med. Chem. 1987, 30, 374. (g) S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner, and F-S. Han, ibid 1987, 30, 976. (h) J. B. Hester, D. H. Plas, H. H. Saneii, T. K. Sawyer, H. J. Schostarez, R. E. Tenbrink, and S. Thaisrivongs, Eur. Pat. Appl. EP 173481 A2, 5 Mar, 1986. (i) P. K. Chakravarty, S. E. de Laszlo, C. S. Sarnella, J. P. Springer, and P. F. Schuda, Tetrahedron Lett. 1989, 30, 415. (j) P. Herold, R. Duthaler, G. Rihs, and C. Angst, J. Org. Chem. 1989, 54, 1178. (k) T. Nishi, M. Kataoka, Y. Morisawa, Chem. Lett. 1989, 1993.

7. S. Valverde, B. Herradon, R. M. Rabanal, and M. Martin-Lomas, Can. J. Chem. 1987, 65, 339.
8. R. J. Ferrier and N. Prasad, J. Chem. Soc. (C) 1969, 570.
9. If the reaction was carried out in EtOH, 9 and 10 were obtained in 36% and 48% yield, respectively.
10. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, Tetrahedron Lett. 1977, 1977.
11. The structure 15a was confirmed by X-ray crystallographic analysis.
12. Y. Morisawa, M. Kataoka, Y. Yabe, Y. Iijima, H. Takahagi, H. Koike, T. Kokubu, Jpn. Kokai Tokkyo Koho, JP H1-199994, 11 Aug 1989.
13. H. J. Bestmann and O. Kratzer, Chem. Ber. 1963, 96, 1899.
14. Tables of atomic coordinates, thermal parameters, bond lengths and bond angles for 18 and 15a are available upon request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CV2 1EW, U. K. Requests should be accompanied by the full literature citation for this article.
15. P. Main, G. Germain, M. M. Woolfson, MULTAN84, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. University of York, England and Louvain, Belgium, 1984.