PEPTIDE INHIBITORS OF ASPARTIC PROTEINASES WITH HYDROXYETHYLENE ISOSTERE REPLACEMENT OF PEPTIDE BOND. I. PREPARATION OF FOUR DIASTEREOISOMERIC (2*R* OR 2*S*,4*R* OR 4*S*,5*S*)-2-BENZYL-5-[(*tert*-BUTOXYCARBONYL)AMINO]-4-HYDROXY-6-PHENYLHEXANOIC ACIDS

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By two separate routes were prepared four diastereoisomers of (2*R* or 2*S*,5*R* or 5*S*)-3-benzyl-5-{(1*S*)-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-ones (**11**, **12**, **17** and **18**). Since the furanones were derived from (*S*)-phenylalanine, absolute configurations of all chiral carbon atoms could be deduced from their ^{1}H NMR spectra. The furanones were easily hydrolyzed to four (2*R* or 2*S*,4*R* or 4*S*,5*S*)-2-benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylbutanoic acids (**20**–**23**), hydroxyethylene isosteres of Phe–Phe peptide bond.

Key words: Hydroxyethylene isostere; γ-Lactones; 5-Amino-2-benzyl-4-hydroxy-6-phenylhexanoic acids; Diastereoisomers; Transition state analogues; Peptidomimetics.

Design of the major part of up to now synthesized aspartic proteinases inhibitors is based on the replacement of the scissile amide bond in short peptide substrates by a nonhydrolyzable isostere (*e.g.*, methyleneamine, hydroxyethylamine, hydroxyethylene; for a review, see *e.g.* ref.[1]). Inhibitors with a hydroxyethylene (H.E.) isostere [$CH(OH)CH_2$] in P1–P1′ position are generally found to be most active because of structural similarity of their complexes with aspartic proteinases to the transition state of hydrolysis of the natural substrate amide bond[2]. The active site pocket of those enzymes is usually hydrophobic and accepts preferentially amino acids with bulky side chains[3], such as phenylalanine, leucine and proline. It is believed that only *S*-configurations both at amino and hydroxy carbon atoms of the dipeptide with hydroxyethylene

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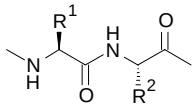
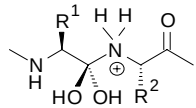
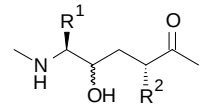
isostere are crucial for potent inhibition of aspartic proteinases. Less is known about the effect of configuration on the third asymmetric carbon of hydroxyethylene isostere on inhibition activity.



Peptide

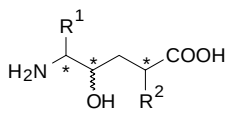


Tetrahedral intermediate



Hydroxyethylene isostere

Hydroxy amino acids **1**, P1–P1′ part of pseudopeptide inhibitors, are usually prepared *via* butyrolactone* **2**. Since carbon backbones of both acid **1** and lactone **2** have three asymmetric carbon atoms, eight diastereoisomers are inherent. However, the configuration at the carbon bearing amino group is derived from a proteinogenic amino acid of *S*-configuration and thus the number of possible diastereoisomers is reduced to four. Numerous synthetic routes leading to acids **1**, with different substituents and of different stereochemistry, have been reported but only two research groups succeeded in preparing all four H.E. diastereomers. Dreyer[4a] and Sakurai[4b] synthesized Phe[H.E.]Pro isosteres; Japanese authors[4b] also described inhibitors with all four Phe[H.E.]Ala isosteres. However, full experimental and spectral data on any homogeneous set of optically pure diastereoisomers of lactones **2** are missing.



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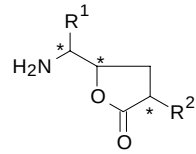


2

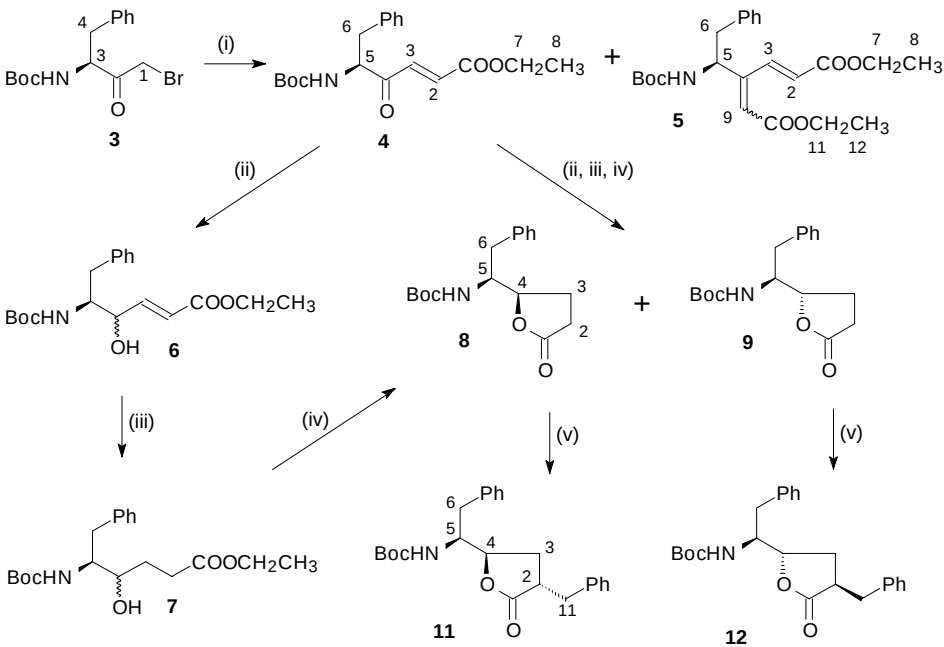
In this paper we present synthesis of four diastereoisomeric lactones **2** (R = R′ = Ph) and hydroxy amino acids **1** (R = R′ = Ph) derived from L-phenylalanyl-L-phenylalanine dipeptide unit which we found effective both in protease substrates[5] and inhibitors[6].

Synthetic strategies leading to lactones with *trans*-oriented substituents at α- and γ-carbons (*trans*-lactones) significantly differ from those affording *cis*-lactones in later stages of the synthesis. The carbon backbone of *trans*-lactones was constructed from

* For brevity, we use throughout the paper the lactone nomenclature instead of rigorous, but less common, tetrahydrofuranone nomenclature. For description of NMR signals, the lactone numbering was also used (see Scheme 1).

phenylalanine by three elongation steps: $C_1 + C_2 + C_n$ (*e.g.*, ref.[7]), for *cis*-lactones only two steps, C1 + C_{n+2}, were required (*e.g.*, ref.[8]).

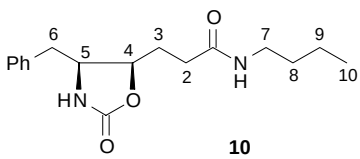
To prepare *trans*-lactones **11** and **12** (Scheme 1), we transformed Boc-phenylalanine *via* a diazo ketone to bromo ketone **3**. The Bestmann reaction[9] of [(ethoxycarbonyl)methylidene]triphenylphosphorane with bromo ketone **3** led to the desired unsaturated keto ester **4** of *E*-configuration, accompanied by diester **5**. The sodium borohydride reduction of keto ester **4** afforded a mixture of diastereomeric unsaturated alcohols **6** in the 2 : 1 ratio, in favor of the 4*R* isomer. Hexanoic acid **7** was obtained by hydrogenation of double bond in **6** on Pd/C. No attempt was made at separation of diastereomers at this point of synthesis and the crude ester was converted by heating in acid medium to a mixture of lactones **8** and **9**; individual diastereoisomers were separated by flash chromatography. The absolute configuration at C-4 of the lactone **8** was deduced from ^{1}H NMR spectra of oxazolidinone **10**. This was prepared in two steps: the opening of lactone **8** with butylamine led to hexanoic acid butylamide which was in the next step cyclized with sodium hydride to oxazolidinone **10**. The value of coupling constant between H-4 and H-5 hydrogens, $J(4,5) = 7.6$ Hz, was characteristic of *cis*-arrange-

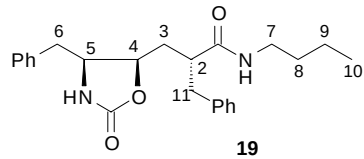


(i) Ph_3P=CHCOOEt, C_6H_6; (ii) $NaBH_4$, EtOH; (iii) H_2,Pd/C, AcOEt; (iv) AcOH, toluene, refl.; (v) 1. BuLi, $(Me_3Si)_2NH$, hexane; 2. $PhCh_2Br$, THF, -78°C.

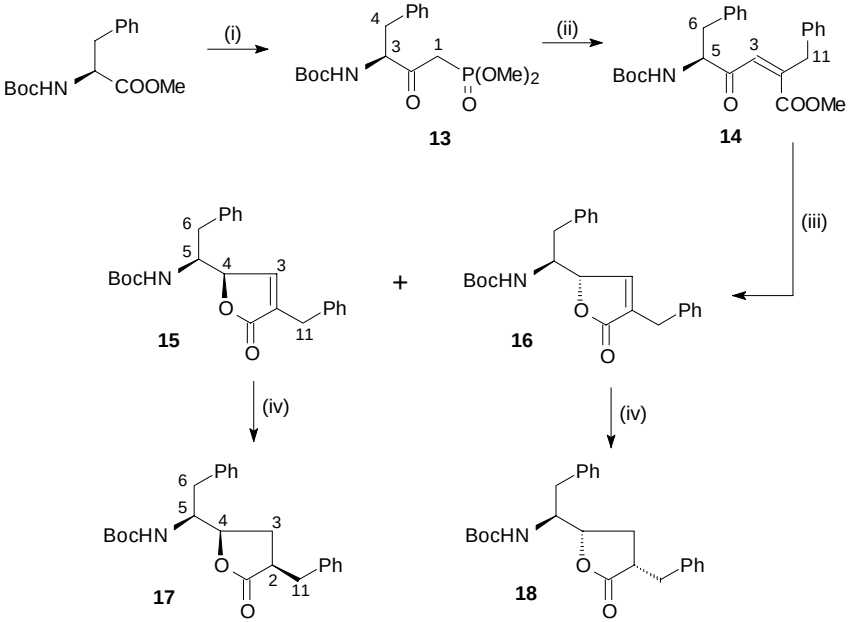
SCHEME 1

ment of vicinal hydrogens in a five-membered ring and was also in good agreement with published data on other differently substituted *cis*-oxazolidinones (see, *e.g.*, ref.[10]). Since the configuration of C-5 is *S*, it follows that the configuration on C-4 in oxazolidinone **10** must be *R*. *trans*-α-Benzyl lactones **11** and **12** were prepared by diastereoselective alkylation of corresponding enolate anions[11], derived from lactones **8** and **9**, with benzyl bromide.





For the synthesis of *cis*-lactones, Chakravarty's procedure[8] was adapted (Scheme 2). Claisen condensation of *N*-Boc-phenylalanine methyl ester and dimethyl methylphosphonate afforded keto phosphonate **13**. Lithium hexamethyldisilanide transformed keto phosphonate **13** to an enolate anion which reacted with methyl 2-oxo-4-phenylbuta-



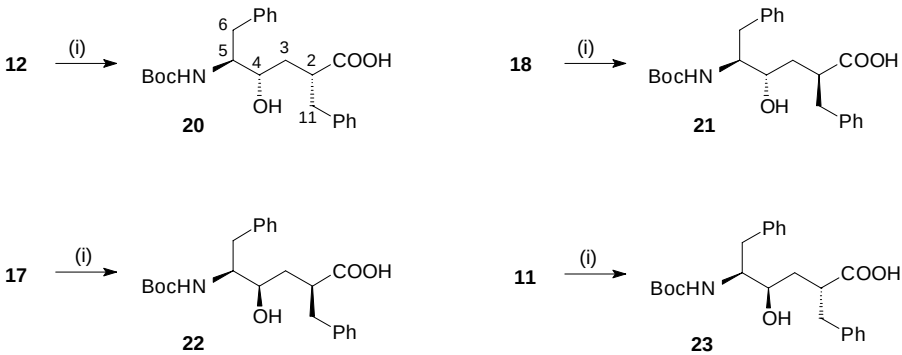
(i) BuLi, $CH_3P(O)(OMe)_2$, THF, -78°C; (ii) BuLi, $(Me_3Si)_2NH$, $PhCH_2COCOOMe$; (iii) $NaBH_4$, MeOH; (iv) H_2, Pd/C, EtOH.

SCHEME 2

noate to unsaturated keto ester **14**. The sodium borohydride reduction of its carbonyl group yielded directly a mixture of unsaturated lactones **15** and **16**. Separation of both diastereoisomers was achieved by repeated silica gel chromatography and crystallization. Pd/C catalyzed addition of hydrogen to the double bond of both isomers proceeded with high diastereoselectivity giving optically pure *cis*-lactones **17** and **18**, after single crystallization.

Absolute configuration at C-4 and C-5 of lactone **17** (Scheme 2) was determined by analysis of ^{1}H NMR spectrum of oxazolidinone **19** which was prepared in the same way as oxazolidinone **10**. The value of coupling constant between H-4 and H-5, $J(4,5)$ = 7.6 Hz, was identical with the $J(4,5)$ coupling constant for oxazolidinone **10**. The conclusion must be also identical: substituents on C-4 and C-5 of oxazolidinone **19** are mutually *cis*-oriented and since the configuration of C-5 is *S*, the configuration on C-4 must be *R*. Configuration on C-2 of *cis*-lactones **17** and **18** was inferred from the presence of nuclear Overhauser effect, while on the contrary, in *trans*-lactones **11** and **12** NOE was not observed. Stereochemical conclusions based on ^{1}H NMR data were confirmed[12] by single crystal X-ray analysis of lactone **18**.

Lactones **11**, **12**, **17** and **18** were finally hydrolyzed to corresponding hydroxy acids **20**–**23** (Scheme 3) with sodium hydroxide in aqueous dioxane[13].



(i) aq. NaOH, dioxane

SCHEME 3

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus. The temperature data are uncorrected. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on Varian Unity 500 spectrometer at 499.8 MHz (FT mode), ^{13}C NMR spectra at 125.7 MHz, both in deuteriochloroform, unless stated otherwise. Tetramethylsilane was used as an internal standard. Optical rotations were determined on a Perkin–Elmer 241 polarimeter at 20–25 °C. IR spectra (ν, cm^{-1}) were measured in chloroform (unless stated otherwise) on a Bruker IFS 88 spectrometer. Mass spectra were recorded on a ZAB-EQ

(VG Analytical) instrument using the EI (70 eV), FAB (Xe, 8 kV) or LSI MS (Cs^+, 35 kV) techniques.

Flash chromatography was carried out on a silica gel 60–120 μm. Thin-layer chromatography was performed on silica gel plates (Silica gel 60 G, Merck and Silufol, Kavalier). Elution was in most cases accomplished by following solvent mixtures: S1, isooctane–dichloromethane–ethyl acetate (15 : 15 : 1); S2, petroleum ether–ethyl acetate–methanol–acetic acid (80 : 5 : 4 : 1); S3, petroleum ether–ethyl acetate–methanol–acetic acid (40 : 15 : 4 : 1). Spot detection was carrried out by spraying with the following reagents: 2% solution of $Ce(SO_4)_2$ in 1 M sulfuric acid followed by pyrolysis; 1% solution of ninhydrin in ethanol followed by heating to 100 °C.

Analytical HPLC were performed on a Spectra Physics instrument with a Vydac 218TP54 column, 25 × 0.4 cm, flow rate 1 ml/min, linear gradient from 100% phase A (0.05% TFA in 50% aqueous MeOH) to 100% phase B (0.05% TFA in MeOH) in 25 min and UV detector setting at 222 nm. Preparative HPLC was performed on a Vydac 218TP510 column, 25 × 0.8 cm, flow rate 3 ml/min, linear gradient from 0.05% TFA in H_2O to 0.05% TFA in 70% aqueous MeOH in 70 min.

(3*S*)-1-Bromo-3-[(*tert*-butoxycarbonyl)amino]-4-phenylbutan-2-one (**3**)

Bromomethyl ketone **3** was prepared according to ref.[14] in 81% yield as white crystals, m.p. 100–104 °C (*t*-BuOMe–hexane), $[\alpha]_D$ –40.2° (*c* 0.52, MeOH). IR: 1 455 (arom.), 1 496 (amide II), 1 603 (arom.), 1 706 (C=O, carbamate), 3 435 (NH). FAB MS, *m/z* (rel.%): 342 (M + H, 6), 288 (25), 286 (25), 264 (14), 262 (14), 244 (27), 242 (30), 220 (19), 208 (40), 185 (48), 164 (100). ^{1}H NMR: 1.41 s, 9 H $(CH_3)_3C$; 3.02 dd, 1 H, *J*(3,4a) = 7.1, *J*(4a,4b) = 13.9 (H-4a); 3.10 dd, 1 H, *J*(3,4b) = 6.6, *J*(4a,4b) = 13.9 (H-4b); 3.84 d, 1 H, *J*(1a,1b) = 13.7 (H-1a); 3.95 d, 1 H, *J*(1a,1b) = 13.7 (H-1b); 4.72 ddd, 1 H, *J*(3,4b) = 6.6, *J*(3,4a) = 7.1, *J*(3,NH) = 7.1 (H-3); 5.04 bd, 1 H, *J*(NH,3) = 7.1 (NH); 7.17 m, 2 H (arom.); 7.26 m, 1 H (arom.); 7.32 m, 2 H (arom.). ^{13}C NMR: 28.22 q ($(\mathbf{C}H_3)_3C$); 33.07 t (C-1); 37.90 t (C-4); 58.51 d (C-3); 80.49 s ($(CH_3)_3\mathbf{C}$); 127.32 d (arom.); 128.92 d (arom.); 129.16 d (arom.); 135.31 s (arom.); 155.23 s ($(CH_3)_3CO\mathbf{C}$=O); 200.85 s (C-2).

Ethyl (5*S*,2*E*)-5-[(*tert*-Butoxycarbonyl)amino]-4-oxo-6-phenylhex-2-enoate (**4**)

Bromomethyl ketone **3** (11.63 g, 34 mmol) and [(ethoxycarbonyl)methylidene]triphenylphosphorane (23.67 g, 68 mmol) were dissolved in benzene (100 ml) and refluxed for 60 min. Reaction mixture was then cooled to 0 °C and crystals of [(ethoxycarbonyl)methylene]triphenylphosphonium bromide were filtered off, washed with benzene and dried *in vacuo* (12.09 g, 83%). Copper(I) chloride (3.36 g, 34 mmol) was then added to the filtrate and the mixture was stirred for 20 min at room temperature. Insoluble residue was filtered off and the solvent was evaporated. The brown-green oily residue was suspended in methanol (100 ml) and precipitated white crystals of $(Ph_3P)_2$·CuCl·Cu (3.93 g, 5.7 mmol) were filtered off and washed with methanol. Combined filtrates were evaporated and the residue was chromatographed on a silica gel column (ether–petroleum ether 1 : 9). Keto ester **4** (2.87 g, 24%) was obtained as crystals, m.p. 79–80.5 °C, $[\alpha]_D$ –62.4° (*c* 0.48, MeOH). FAB MS, *m/z* (rel.%): 348 (M + H, 9), 292 (63), 248 (100), 154 (61), 120 (42), 91 (53). IR: 1 495, 1 600 (arom.), 1 705 (C=O), 3 435 (NH). ^{1}H NMR: 1.32 t, 3 H, *J*(8.7) = 7.1 (H-8); 1.41 s, 9 H ($(CH_3)_3C$); 3.01 dd, 1 H, *J*(5,6a) = 6.1, *J*(6a,6b) = 14.2 (H-6a); 3.16 dd, 1 H, *J*(5,6b) = 6.3, *J*(6a,6b) = 14.2 (H-6b); 4.26 q, 2 H, *J*(7,8) = 7.1 (H-7); 4.79 bq, 1 H, *J*(5,6a) = 6.1 (H-5); 5.13 bd, 1 H, *J*(NH,5) = 7.1 (NH); 6.75 d, 1 H, *J*(2,3) = 15.9 (H-2); 7.15 d, 1 H, *J*(3,2) = 15.9 (H-3); 7.10–7.29 m, 5 H (arom.). ^{13}C NMR: 14.07 q (C-8); 28.25 q ($(\mathbf{C}H_3)_3C$); 37.35 t (C-6); 59.64 d (C-5); 61.45 t (C-7); 80.19 s ($(CH_3)_3\mathbf{C}$); 127.18 d (arom.); 128.69 d (arom.); 129.37 d (arom.); 132.32 d (C-2); 135.51 s (arom.); 136.22 d (C-3); 155.11 s ($(CH_3)_3CO\mathbf{C}$=O); 165.13 s (C-1); 197.38 (C-4). For $C_{19}H_{25}NO_5$ (347.4) calculated: 65.68% C, 7.25% H, 4.03% N; found: 65.41% C, 7.32% H, 4.26% N.

From more polar fractions, 5.68 g (40%) of diethyl 3-{(1*S*)-11[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}hexa-2,4-diene-1,6-dioate (**5**) was isolated, m.p. 129–131 °C, $[\alpha]_D$ +56.1° (*c* 0.43, MeOH). FAB MS, *m/z* (rel.%): 418 (M + H, 4), 362 (15), 318 (65), 272 (100), 120 (20). IR: 1 497, 1 604 (arom.), 1 634 (C=C), 1 712 (C=O), 3 443 (NH). ^{1}H NMR: 1.30 t, 3 H, *J*(8,7) = 7.1 (H-8); 1.32 t, 3 H, *J*(12,11) = 7.1 (H-12); 1.36 s, 9 H ($(CH_3)_3CO$); 2.75 dd, 1 H, *J*(6a,5) = 8.1, *J*(6a,6b) = 14.2 (H-6a); 3.05 dd, 1 H, *J*(6b,5) = 5.1, *J*(6a,6b) = 14.2 (H-6b); 4.23 q, 4 H, *J*(7,8) = *J*(11,12) = 7.1 (2 × H-7 and 2 × H-11); 4.66 m, 1 H (H-5); 4.84 bs, 1 H (NH); 6.34 bd, 1 H, *J*(2,3) = 16.1 (H-2); 7.07–7.43 m, 5 H (arom.); 8.48 d, 1 H, *J*(3,2) = 16.1 (H-3). ^{13}C NMR: 14.16 q + 14.22 q (C-8 + C-12); 28.19 q ($(\mathbf{C}H_3)_3C$); 40.69 t (C-6); 52.81 d (C-5); 60.65 + 60.79 q (C-7 + C-11); 80.10 s ($(CH_3)_3\mathbf{C}$); 121.44 d (C-2 + C-9); 127.11 d (arom.); 128.72 d (arom.); 129.12 d (arom.); 129.21 d (C-3); 136.16 s (arom.); 138.71 s (C-4); 154.67 s ($(CH_3)_3CO\mathbf{C}$=O); 165.40 + 166.27 s (C-1 + C-10). For $C_{23}H_{31}NO_6$ (417.5) calculated: 66.16% C, 7.48% H, 3.35% N; found: 65.96% C, 7.54% H, 3.70% N.

Ethyl (2*E*,4*RS*,5*S*)-5-[(*tert*-Butoxycarbon yl)amino]-4-hydroxy-6-phenylhex-2-enoate (**6**)

To the keto ester **4** (2.87 g, 8.27 mmol) dissolved in ethanol (50 ml), sodium borohydride (0.63 g, 16.5 mmol) was added at room temperature. After 15 min TLC showed the reaction to be complete. The excess of borohydride was decomposed by acetone (1 ml) and the reaction mixture was evaporated. The residue was dissolved in ethyl acetate, extracted with 5% $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated. A mixture of diastereoisomeric hydroxy esters 6 (2.57 g, 89%) was obtained in the ratio 2 : 1 (4*R*/4*S*). The major isomer (more polar on silica gel) was isolated by careful chromatography and repeated crystallization.

Major isomer (2*E*,4*R*,5*S*)-**6**: M.p. 120–124 °C, $[\alpha]_D$ +4.4° (*c* 0.45, MeOH). SIMS MS, *m/z* (rel.%): 350 (M + H, 13), 295 (39), 250 (26), 214 (19), 164 (51), 120 (199). ^{1}H NMR: 1.30 t, 3 H, *J*(8,7) = 7.1 (H-8); 1.38 s, 9 H ($(CH_3)_3CO$); 2.78 dd, 1 H, *J*(6a,5) = 9.0, *J*(6a,6b) = 14.2 (H-6a); 2.83 dd, 1 H, *J*(6b,5) = 6.0, *J*(6a,6b) = 14.2 (H-6b); 3.83 m, 1 H (H-4); 4.22 q, 2 H, *J*(7.8) = 7.1 (H-7); 4.44 m, 1 H (H-5); 4.63 bd, 1 H, *J*(NH,5) = 8.0 (NH); 6.17 dd, 1 H, *J*(2,3) = 15.6, *J*(2,4) = 1.8 (H-2); 6.99 dd, 1 H, *J*(3,4) = 4.6, *J*(3,2) = 15.6 (H-3); 7.18–7.33 m, 5 H (arom.). For $C_{19}H_{27}NO_5$ (349.4) calculated: 65.30% C, 7.78% H, 4.00% N; found: 65.12% C, 7.79% H, 4.06% N.

Minor isomer (2*E*,4*S*,5*S*)-**6**: ^{1}H NMR: 1.27 t, 3 H, *J*(8,7) = 7.1 (H-8); 1.38 s, 9 H ($(CH_3)_3CO$); 2.95 m, 2 H (H-6); 3.86 m, 1 H (H-4); 4.18 q, 2 H, *J*(7,8) = 7.1 (H-7); 4.40 m, 1 H (H-5); 4.84 bd, 1 H, *J*(NH,5) = 8.7 (NH); 6.08 bd, 1 H, *J*(2,3) = 15.6, *J*(2,4) > 0.0 (H-2); 6.92 dd, 1 H, *J*(3,4) = 4.4, *J*(3,2) = 15.6 (H-3); 7.18–7.33 m, 5 H (arom.).

Ethyl (4*RS*,5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoate (**7**)

Diastereoisomeric mixture of unsaturated hydroxy acids **6** (2.50 g, 7.16 mmol) was dissolved in ethyl acetate and 5% palladium on charcoal (0.5 g) was added. Hydrogen was passed through the stirred suspension in a hydrogenation flask for 4 h. The catalyst was filtered off and the filtrate was evaporated. The white residue (2.29 g, 91%) was used without further purification for preparation of lactones **8** and **9**. FAB MS, *m/z* (rel.%): 352 (M + H, 33), 296 (35), 278 (12), 252 (94), 234 (29), 210 (25), 164 (19), 120 (61), 91 (100). ^{1}H NMR: 1.26 t, 3 H, *J*(8,7) = 7.1 (H-8); 1.36 s, 9 H $(CH_3)_3CO$); 1.80 m, 2 H (H-3); 2.53 m, 2 H (H-2); 2.80 dd, 1 H, *J*(6a,5) = 7.3, *J*(6a,6b) = 14.2 (H-6a); 3.02 dd, 1 H, *J*(6b,5) = 4.4, *J*(6a,6b) = 14.2 (H-6b); 3.57 m, 1 H (H-4); 4.24 q, 2 H, *J*(7,8) = 7.1 (H-7); 4.37 m, 1 H (H-5); 4.59 bd, 1 H, *J*(NH,5) = 7.5 (NH); 7.17–7.38 m, 5 H (arom.). For $C_{19}H_{29}NO_5$ (351.4) calculated: 64.93% C, 8.31% H, 3.98% N; found: 65.23% C, 8.34% H, 4.02% N.

(5*RS*)-5-{(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-ones **8** and **9**

Mixture of diastereomeric saturated hydroxy acids **7** (0.50 g, 1.42 mmol) was dissolved in toluene (50 ml) and acetic acid (1 ml) and refluxed for 3 h. The solution was evaporated to dryness and diastereoisomeric lactones were separated on silica gel column (35 to 50% ether in petroleum ether).

(5S)-5-{(1S)-1-[(tert-Butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**9**): Yield 26%, m.p. 157–158 °C, $[\alpha]_D$ –18.3° (*c* 0.66, MeOH). FAB MS, *m/z* (rel.%): 306 (M + H, 5), 250 (100), 232 (10), 206 (71), 120 (25), 91 (39), 57 (58). ^{1}H NMR: 1.39 bs, 9 H ($(CH_3)_3CO$); 2.07–2.18 m, 2 H (H-3); 2.49 dt, 1 H, *J*(2a,3a) = 9.3, *J*(2a,3b) = 9.3, *J*(2a,2b) = 18.0 (H-2a); 2.54 ddd, 1 H, *J*(2b,3b) = 5.6, *J*(2b,3a) = 9.3, *J*(2a,2b) = 18.0 (H-2b); 2.88 dd, 1 H, *J*(6a,5) = 8.9, *J*(6a,6b) = 13.7 (H-6a); 2.96 dd, 1 H, *J*(6b,5) = 7.1, *J*(6a,6b) = 13.7 (H-6b); 4.01 bq, 1 H, *J*(5,4) = 0.7, *J*(5,6b) = 8.7, *J*(5,6a) = 8.7, *J*(5,NH) = 8.7 (H-5); 4.48 dt, 1 H, *J*(4,5) = 0.7, *J*(4,3a) = 7.5, *J*(4,3b) = 7.5 (H-4); 4.61 bd, 1 H, *J*(NH,5) = 8.7 (NH); 7.21–7.33 m, 5 H (arom.). ^{13}C NMR: 24.15 t (C-3); 28.23 q (($\mathbf{C}H_3)_3C$); 28.71 t (C-2); 39.41 t (C-6); 54.07 d (C-5); 79.88 d (C-4); 80.01 s (($(CH_3)_3\mathbf{C}$); 126.75 d (arom.); 128.65 d (arom.); 129.34 d (arom.); 137.16 s (arom.); 155.85 s (CONH); 177.17 s (C-1).

(5R)-5-{(1S)-1-[(tert-Butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**8**): Yield 46%, m.p. 130–133 °C, $[\alpha]_D$ –21.3° (*c* 0.51, MeOH). FAB MS, *m/z* (rel.%): 328 (M + Na, 8), 306 (M + H, 6), 250 (100), 232 (7), 206 (26), 154 (34), 120 (15), 91 (25), 57 (37). IR: 1 455 (arom.), 1 501 (amide II), 1 604 (arom.), 1 709 (C=O, carbamate), 1 777 (C=O, lactone), 3 435 (NH). ^{1}H NMR: 1.36 bs, 9 H ($(CH_3)_3CO$); 2.12 m, 1 H, *J*(3a,4) = 7.4, *J*(3a,2a) = 9.6, *J*(3a,2b) = 9.6, *J*(3a,3b) = 12.4 (H-3a); 2.28 dddd, 1 H, *J*(3b,2b) = 5.5, *J*(3b,4) = 7.4, *J*(3b,2a) = 9.6, *J*(3a,3b) = 12.4 (H-3b); 2.53 dt, 1 H, *J*(2a,3b) = 9.6, *J*(2,3) = 9.6, *J*(2a,2b) = 17.9 (H-2a); 2.60 ddd, 1 H, *J*(2b,3b) = 5.5, *J*(2b,3a) = 9.6, *J*(2a,2b) = 17.9 (H-2b); 2.87 bdd, 1 H, *J*(6a,5) = 7.6, *J*(6a,6b) = 13.9 (H-6a); 3.02 dd, 1 H, *J*(6b,5) = 4.5, *J*(6a,6b) = 13.9 (H-6a); 3.02 dd, 1 H, *J*(6b,5) = 4.5, *J*(6a,6b) = 13.9 (H-6b); 3.98 m, 1 H (H-5); 4.39 bq, 1 H, *J*(4,5) = 7.4, *J*(4,3a) = 7.4, *J*(4,3b) = 7.4 (H-4); 4.45 bd, 1 H, *J*(NH,5) = 7.5 (NH); 7.20–7.34 m, 5 H (arom.). ^{13}C NMR: 24.64 t (C-3); 28.20 q (($\mathbf{C}H_3)_3C$); 29.67 t (C-2); 36.38 t (C-6); 53.93 d (C-5); 80.71 d (C-4); 79.95 s (($(CH_3)_3\mathbf{C}$); 126.80 d (arom.); 128.65 d (arom.); 129.57 d (arom.); 136.44 s (arom.); 155.39 s ($(CH_3)_3CO\mathbf{C}$=O); 176.77 s (C-1). For $C_{17}H_{23}NO_4$ (305.4) calculated: 66.86% C, 7.59% H, 4.58% N; found: 66.20% C, 7.50% H, 4.50% N.

(2*S*,5*R*)-3-Benzyl-5-{(1*S*)-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**11**)

A mixture of THF (5 ml) and hexamethyldisilazane (1.38 ml, 6.6 mmol) was cooled to 0 °C. At this temperature, 1.6 M solution of butyllithium in hexanes was added (3.78 ml, 6.0 mmol). The reaction mixture was cooled to –78 °C and a solution of lactone 8 (0.92 g, 3.0 mmol) in THF (5 ml) was added. After stirring for 1 h, a solution of benzyl bromide (0.36 ml, 3.0 mmol) in THF (2 ml) was slowly added and the mixture was stirred for 90 min. The ethanol bath was allowed to warm to –40 °C and the reaction was quenched with acetic acid (1 ml). The solution was diluted with *t*-BuOMe, washed with aqueous 10% citric acid, 10% $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated in vacuum. Chromatography on silica gel (15–30% ether in petroleum ether) afforded 0.56 g (47%) of **11**, white crystals, m.p. 135–137 °C, $[\alpha]_D$ –18.2° (*c* 0.52, MeOH). IR: 1 455 (arom.), 1 497 (amide II), 1 604 (arom.), 1 708 (C=O, carbamate), 1 772 (C=O, lactone), 3 436 (NH). FAB MS, m/s (rel.%): 418 (M + Na, 6), 396 (M + H, 9), 340 (100), 322 (13), 296 (14). ^{1}H NMR: 1.33 bs, 9 H ($(CH_3)_3CO$); 2.00 bdt, 1 H, *J*(3a,2) = 7.6, *J*(3a,4) = 7.6, *J*(3a,3b) = 13.6 (H-3a); 2.17 ddd, 1 H, *J*(3b,4) = 4.7, *J*(3b,2) = 9.3, *J*(3b,3) = 13.6 (H-3b); 2.81 bdd, 2 H, *J*(6a,5) = 9.1 (H-6a); 2.96 dd, 1 H, *J*(11a,2) = 4.0, *J*(11a,11b) = 14.1 (H-11a); 3.06 bs, 1 H (H-2); 3.17 dd, 1 H, *J*(11b,2) = 4.0, *J*(11a,11b) = 14.1 (H-11b); 3.90 bs, 1 H (H-5); 4.12 bs, 1 H (H-4); 4.34 bd, 1 H, *J*(NH,5) = 9.0 (NH); 7.14–7.32 m, 10 H (arom.). ^{13}C NMR: 28.15 q (($\mathbf{C}H_3)_3C$); 29.27 t (C-3); 36.37 t (C-11); 36.37 t (C-6); 40.39 d (C-2); 53.50 d (C-5); 78.60 d (C-4); 79.96 s (($(CH_3)_3\mathbf{C}$); 126.73 d (arom.); 126.83 d (arom.); 128.70 d

(arom.); 128.70 d (arom.); 128.94 d (arom.); 129.56 d (arom.); 136.28 s (arom.); 137.86 s (arom.); $((CH_3)_3CO\mathbf{C}{=}O)$ and (C-1) signals were hidden in noise. For $C_{24}H_{29}NO_4$ (395.5) calculated: 72.88% C, 7.39% H, 3.54% N; found: 72.90% C, 7.47% H, 3.51% N.

(2*R*,5*R*)-3-Benzyl-5-{(1*S*)-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**12**)

Lactone **12** was prepared in a manner analogous to lactone **11**. Yield 22%, oil, $[\alpha]_D$ –14.2° (*c* 0.37, MeOH). IR: 1 455 (arom.), 1 497 (amide II), 1 604 (arom.), 1 708 (C=O, carbamate), 1 767 (C=O, lactone), 3 436 (NH). ^{1}H NMR: 1.35 s, 9 H ($(CH_3)_3CO$); 1.96 ddd, 1 H, *J*(3a,2) = 6.3, *J*(3a,4) = 8.0, *J*(3a,3b) = 13.7 (H-3); 2.21 ddd, 1 H, *J*(3b,4) = 5.6, *J*(3b,2) = 9.7, *J*(3a,3b) = 13.7 (H-3b); 2.77 dd, 1 H, *J*(11a,2) = 9.0, *J*(11a,11b) = 14.0 (H-11a); 2.82 dd, 1 H, *J*(6a,5) = 8.5, *J*(6a,6b) = 13.5 (H-6a); 2.87 dd, 1 H, *J*(6a,5) = 7.3, *J*(6a,6b) = 13.5 (H-6b); 2.97 m, 1 H, *J*(2,11b) = 4.6, *J*(2,3a) = 6.3, *J*(2,11a) = 9.0, *J*(2,3b) = 9.7 (H-2); 3.11 dd, 1 H, *J*(11b,2) = 4.6, *J*(11a,11b) = 14.0 (H-11b); 3.93 bq, 1 H, *J* = 9.0 (H-5); 4.20 ddd, 1 H, *J*(4,5) = 1.5, *J*(4,3b) = 5.6, *J*(4,3a) = 8.0 (H-4); 4.52 bd, 1 H, *J*(NH,5) = 9.5 (NH); 7.12–7.31 m, 10 H (arom.). ^{13}C NMR: 28.19 q ($(\mathbf{C}H_3)_3C$); 29.33 t (C-3); 36.91 t (C-11); 39.05 t (C-6); 41.34 d (C-2); 54.52 d (C-5); 78.27 d (C-4); 80.03 s ($(CH_3)_3\mathbf{C}$); 126.72 d (arom.); 126.90 d (arom.); 128.64 d (arom.); 128.70 d (arom.); 128.84 d (arom.); 129.27 d (arom.); 137.07 s (arom.); 137.83 s (arom.); 155.81 s ($(CH_3)_3CO\mathbf{C}{=}O$); 179.12 s (C-1).

Dimethyl (3*S*)-{3-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-2-oxobutyl}phosphonate (**13**)

Solution of dimethyl methylphosphonate (16.3 ml, 150 mmol) in THF (50 ml) in a nitrogen atmosphere was cooled to –78 °C and in 15 min 1.6 M solution of butyllithium in hexanes (94 ml, 150 mmol) was added. The solution was stirred for additional 5 min and a solution of *N*-Boc-L-phenylalanine methyl ester (6.98 g, 25 mmol) in THF (100 ml) was added in 1 h. The reaction mixture was then stirred at –78 °C for 1 h and at –30 °C for 1 h.The reaction was quenched with acetic acid (0.7 ml) and the content of the reaction vessel was slowly poured into a saturated aqueous solution of $NaHCO_3$ (200 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). Combined ether extracts were washed with 5% $KHSO_4$, 5% $NaHCO_3$ and brine. The solution was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate 1 : 1). Oily phosphonate **13** (7.96 g, 86%) crystallized on standing. M.p. 65–72 °C, $[\alpha]_D$ –12.7° (*c* 1.58, MeOH), R_F 0.40 (S3). FAB MS, *m/z* (rel.%): 372 (M + H, 10), 316 (28), 272 (100), 180 (10), 162 (13), 151 (37), 144 (61), 120 (30), 91 (30), 57 (71). IR: 1 036 (P–OCH_3), 1 252 (P=O), 1 455 (arom.), 1 708 (C=O), 3 434 (NH). ^{1}H NMR: 1.39 s, 9 H ($(CH_3)_3CO$); 2.94 dd, 1 H, *J*(4a,3) = 8.1, *J*(4a,4b) = 14.2 (H-4a); 3.09 dd, 1 H, *J*(1a,1b) = 14.2, *J*(1,P) = 22.4 (H-1a); 3.19 dd, 1 H, *J*(4b,3) = 5.9, *J*(4a,4b) = 14.2 (H-4b); 3.25 dd, 1 H, *J*(1a,1b) = 14.2, *J*(1b,P) = 22.4 (H-1b); 3.76 d, 3 H, *J*(OCH_3,P) = 11.2 (OCH_3); 3.77 d, 3 H, *J*(OCH_3,P) = 11.2 (OCH_3); 4.56 dt, 1 H, *J*(3,4b) = 5.9, *J*(3,4a) = 8.1, *J*(3,NH) = 8.1 (H-3); 5.29 bd, 1 H, *J*(NH,3) = 8.1 (NH); 7.18–7.30 m, 5 H (arom.). ^{13}C NMR: 28.22 q ($(\mathbf{C}H_3)_3C$); 36.93 t (C-4); 38.50 t, *J*(C,P) = 129.9 (C-1); 53.12 12 q (OCH_3); 53.12 q (OCH_3); 61.19 d (C-3); 80.12 s ($(CH_3)_3\mathbf{C}$); 126.92 d (arom.); 128.62 d (arom.); 129.33 d (arom.); 136.46 s (arom.); 155.29 s ($(CH_3)_3CO\mathbf{C}{=}O$); 201.16 s (C-2). ^{31}P NMR: +22.82 (P). For $C_{17}H_{26}NO_6P$ (371.4) calculated: 54.98% C, 7.05% H, 3.77% N, 8.34% P; found: 54.84% C, 7.01% H, 3.71% N, 8.57% P.

Methyl (5*S*,2*Z*)-2-Benzyl-[5-(*tert*-butoxycarbonyl)amino]-4-oxo-6-phenylhex-2-enoate (**14**)

To a solution of phosphonate **13** (14.24 g, 38.3 mmol) in THF (100 ml) in nitrogen atmosphere cooled to –10 °C was added 2 M solution of butyllithium in cyclohexane (18.5 ml, 37 mmol). The mixture was stirred at –10 °C for 1 h and then a solution of methyl 2-oxo-3-phenylpropionate in THF

(100 ml) was slowly added. Stirring was continued at ambient temperature for 2 h. The reaction was quenched with water (150 ml), the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 ml). Organic extracts were combined, washed with water (2 × 30 ml) and brine, dried with $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (chloroform–petroleum ether 1 : 1). Ketone **14**, obtained as a pale yellow oil, crystallized on standing (12.96 g, 80%). M.p. 131–140 °C, R_F 0.60 (S2). FAB MS, *m/z* (rel.%): 424 (M + H, 1), 336 (5), 324 (14), 120 (43), 91 (76), 57 (100). IR: 1 455, 1 497, 1 603 (arom.), 1 624 (C=C), 1 700 (C=O, carbamate), 1 709 (C=O), 3 433 (NH). ^{1}H NMR: 1.39 s, 9 H ($(CH_3)_3CO$); 2.95 dd, 1 H, *J*(6a,5) = 6.4, *J*(6a,6b) = 14.1 (H-6a); 3.04 dd, 1 H, *J*(6b,5) = 6.7, *J*(6a,6b) = 14.1 (H-6b); 3.59 bd, 2 H, J = 1.6 (2 × H-11); 3.72 s, 3 H ($COOCH_3$); 4.60 ddd, 1 H, *J*(5,6a) = 6.4, *J*(5,6b) = 6.7, *J*(5,NH) = 7.8 (H-5); 5.15 bd, 1 H, *J*(NH,5) = 7.8 (NH); 5.85 t, *J*(3,11) = 1.6 (H-3); 7.07–7.13 m, 10 H (arom.). ^{13}C NMR: 28.26 q (($\mathbf{C}H_3)_3C$); 37.89 t (C-6); 39.92 t (C-11); 52.37 q ($COOCH_3$); 60.20 d (C-5); 79.78 s ($(CH_3)_3\mathbf{C}$); 126.90 d (arom.); 127.20 d (arom.); 128.20 d (C-3); 128.49 d (arom.); 128.49 d (arom.); 129.30 d (arom.); 129.44 d (arom.); 135.49 s (arom.); 136.05 s (arom.); 146.74 s (C-2); 155.07 s ($(CH_3)_3CO\mathbf{C}$=O); 168.70 s (C-1); 198.00 s (C-4). For $C_{25}H_{29}NO_5$ (423.5) calculated: 70.90% C, 6.90% H, 3.30% N; found: 70.90% C, 6.95% H, 3.31% N.

(5*RS*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}-2,5-dihydrofuran-2-ones **15** and **16**

Ketone **14** (4.86 g, 11.5 mmol) was dissolved in methanol and the solution was cooled to –30 °C. With stirring, sodium borohydride (0.44 g, 11.5 mmol) was added and the course of reaction was followed by HPLC. When the reduction of ketone was completed, methanol was evaporated in vacuum and the residue was chromatographed on a silica gel column (20 to 24% ether in petroleum ether) to give 1.41 g (31%) of lactone **16**, 0.8 g (18%) of lactone **15** and 0.95 g (21%) of a **15** and **16** mixture which could be separated in the same way again.

(5S)-3-Benzyl-5-{(1S)-1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-2,5-dihydrofuran-2-one (**16**): M.p. 129–132 °C, $[\alpha]_D$ 0.0° (*c* 0.5, MeOH), $[\alpha]_D$ –13.1° (*c* 0.77, $CHCl_3$), R_F 0.35 (S1). FAB MS, *m/z* (rel.%): 394 (M + H, 1), 338 (26), 294 (24), 277 (10), 202 (8), 175 (9), 164 (46), 120 (95), 91 (69), 57 (100). IR: 1 455 (arom.), 1 497 (amide II), 1 652 (C=C), 1 707 (C=O, carbamate), 1 758 (C=O, lactone), 3 442 (NH). ^{1}H NMR: 1.38 s, 9 H ($(CH_3)_3CO$); 2.93 dd, 1 H, *J*(6a,5) = 8.6, *J*(6a,6b) = 13.4 (H-6a); 2.99 dd, 1 H, *J*(6b,5) = 6.7, *J*(6a,6b) = 13.4 (H-6b); 2.98 bd, 1 H, *J*(11a,11b) = 16.2 (H-11a); 3.59 bd, 1 H, *J*(11a,11b) = 16.2 (H-11b); 4.16 dddd, 1 H, *J*(5,4) = 2.6, *J*(5,6b) = 6.7, *J*(5,6a) = 8.6, *J*(5,NH) = 9.5 (H-5); 4.50 bd, 1 H, *J*(NH,5) = 9.5 (NH); 4.80 m, 1 H (H-4); 6.85 bs, 1 H (H-3); 7.10–7.34 m, 10 H (arom.). For $C_{24}H_{27}NO_4$ (393.5) calculated: 73.25% C, 6.92% H, 3.55% N; found: 72.91% C, 7.03% H, 3.50% N.

(5R)-3-Benzyl-5-{(1S)-1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-2,5-dihydrofuran-2-one (**15**): Oil, $[\alpha]_D$ +1.5° (*c* 0.8, MeOH), R_F 0.25 (S1). FAB MS, *m/z* (rel.%): 416 (M + Na, 10), 394 (M + H, 4), 360 (5), 338 (100), 320 (6), 294 (42), 277 (20), 202 (9), 175 (15), 164 (43), 120 (79), 91 (55), 57 (100). ^{1}H NMR: 1.35 s, 9 H ($(CH_3)_3CO$); 2.80 d, 2 H, *J*(6a,6b) = 6.6 (H-6a); 3.54 bd, 1 H, *J*(11a,11b) = 15.9 (H-11a); 3.59 bd, 1 H, *J*(11a,11b) = 15.9 (H-11b); 4.06 m, 1 H (H-5); 4.62 bd, 1 H, *J*(NH,5) = 8.8 (NH); 4.93 bd, 1 H, *J*(4,5) = 4.0 (H-4); 6.74 bs, 1 H (H-3); 7.12–7.36 m, 10 H (arom.). For $C_{24}H_{27}NO_4$ (393.5) calculated: 73.25% C, 6.92% H, 3.55% N; found: 73.02% C, 7.13% H, 3.46% N.

(3*S*,5*S*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**18**)

Lactone **16** (1.24 g, 3.17 mmol) was dissolved in ethanol, 10% Pd/C (0.2 g) was added and through stirred suspension hydrogen was passed until TLC (S1) indicated complete reduction (5.5 h). The catalyst was filtered off and the filtrate evaporated (1.18 g, 94%). Crystallization from *t*-BuOMe–

hexane afforded 0.86 g (69%) of lactone **18**, m.p. 118–120 °C, $[\alpha]_D$ +47.5° (*c* 0.57, $CHCl_3$), $[\alpha]_D$ +47.8° (*c* 0.53, MeOH), R_F 0.30 (S1). FAB MS, *m/z* (rel.%): 396 (M + H, 1), 340 (20), 322 (9), 296 (37), 120 (43), 91 (100), 57 (100). ^{1}H NMR: 1.40 s, 9 H ($(CH_3)_3CO$); 1.80 dt, 1 H, *J*(3b,4) = 10.3, *J*(3b,2) = 11.8, *J*(3a,3b) = 12.4 (H-3b); 2.07 ddd, 1 H, *J*(3a,4) = 5.9, *J*(3a,2) = 8.8, *J*(3a,3b) = 13.0 (H-3a); 2.85 dddd, 1 H, *J*(2,11b) = 4.1, *J*(2,3a) = 8.8, *J*(2,11a) = 9.8, *J*(2,3b) = 11.8 (H-2); 2.85 dd, 1 H, *J*(6a,5) = 9.0, *J*(6a,6b) = 13.6 (H-6a); 2.96 dd, 1 H, *J*(6b,5) = 6.8, *J*(6a,6b) = 13.6 (H-6b); 2.98 dd, 1 H, *J*(11a,2) = 9.8, *J*(11a,11b) = 13.9 (H-11a); 3.26 dd, 1 H, *J*(11b,2) = 4.1, *J*(11a,11b) = 13.9 (H-11b); 3.94 dddd, 1 H, *J*(5,4) = 1.5, *J*(5,6b) = 6.8, *J*(5,6a) = 9.0, *J*(5,NH) = 10.0 (H-5); 4.31 ddd, 1 H, *J*(4,5) = 1.5, *J*(4,3a) = 5.9, *J*(4,3b) = 10.3 (H-4); 4.61 d, 1 H, *J*(NH,5) = 10.0 (NH); 7.12–7.30 m, 10 H (arom.). ^{13}C NMR: 28.24 q ($(\mathbf{C}H_3)_3C$); 30.41 t (C-3); 36.12 t (C-11); 39.34 t (C-6); 42.50 d (C-2); 53.18 d (C-5); 77.68 d (C-4); 79.86 s ($(CH_3)_3\mathbf{C}$); 126.68 d (arom.); 128.60 d (arom.); 128.65 d (arom.); 128.65 d (arom.); 128.68 d (arom.); 129.28 d (arom.); 137.13 s (arom.); 138.31 s (arom.); 155.72 s ($(CH_3)_3CO\mathbf{C}$=O); 177.87 s (C-1). For $C_{24}H_{29}NO_4$ (395.5) calculated: 72.88% C, 7.39% H, 3.54% N; found: 72.63% C, 7.35% H, 3.59% N.

(3*R*,5*R*)-3-Benzyl-5-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}tetrahydrofuran-2-one (**17**)

Isomeric lactone **17** was prepared by the same procedure as lactone **18** in 65% yield. M.p. 127–128.5 °C, $[\alpha]_D$ –78.5° (*c* 0.62, $CHCl_3$), $[\alpha]_D$ –98.1° (*c* 0.48, MeOH), R_F 0.20 (S1). FAB MS, *m/z* (rel.%): 396 (M + H, 3), 340 (53), 322 (14), 296 (30), 278 (10), 120 (50), 91 (100), 57 (100). ^{1}H NMR: 1.35 s, 9 H ($(CH_3)_3CO$); 1.79 dt, 1 H, *J*(3b,4) = 10.9, *J*(3b,2) = 12.5, *J*(3a,3b) = 12.5 (H-3b); 2.23 ddd, 1 H, *J*(3a,4) = 6.2, *J*(3a,2) = 8.8, *J*(3a,3b) = 12.5 (H-3a); 2.90 dddd, 1 H, *J*(2,11b) = 4.2, *J*(2,3a) = 8.8, *J*(2,11a) = 9.8, *J*(2,3b) = 11.8 (H-2); 2.72 dd, 1 H, *J*(11a,2) = 9.8, *J*(11a,11b) = 13.9 (H-11a); 2.82 m, 2 H (H-6); 3.28 dd, 1 H, *J*(11b,2) = 4.1, *J*(11a,11b) = 13.9 (H-11b); 3.90 m, 1 H (H-5); 4.28 m, 1 H (H-4); 4.44 bd, 1 H, *J*(NH,5) = 8.0 (NH); 7.15–7.32 m, 10 H (arom.). ^{13}C NMR: 28.19 q ($(\mathbf{C}H_3)_3C$); 31.34 t (C-3); 36.11 t (C-11); 36.23 t (C-6); 42.49 d (C-2); 54.30 d (C-5); 78.95 d (C-4); 126.71 d (arom.); 128.58 d (arom.); 128.67 d (arom.); 128.81 d (arom.); 129.48 d (arom.); 136.62 s (arom.); 138.38 s (arom.); 155.21 s ($(CH_3)_3CO\mathbf{C}$=O); 177.60 s (C-1). ($(CH_3)_3\mathbf{C}$) signal was hidden in the noise. For $C_{24}H_{29}NO_4$ (395.5) calculated: 72.88% C, 7.39% H, 3.54% N; found: 72.68% C, 7.44% H, 3.46% N.

Preparation of Hydroxy Acids **20**–**23**. General Procedure

Lactone **11**, **12**, **17** or **18** (0.30 g, 0.76 mmol) was dissolved in a dioxane (7.0 ml)–water (3.5 ml) mixture. The solution was stirred at ambient temperature and 1 M sodium hydroxide (0.9 ml, 0.9 mmol) was slowly added. After TLC (S2) indicated complete consumption of a lactone, dioxane was removed in vacuum and the residue was distributed between aqueous 10% citric acid and ether. The aqueous layer was extracted with ether (3 × 5 ml), combined extracts were washed with brine and dried ($MgSO_4$), the solvent was evaporated and the residue was dried in vacuum at 40 °C.

(2*S*,4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoic Acid (**23**)

According to the general procedure, 0.29 g (93%) of hydroxy acid **23** was obtained. M.p. 139–143 °C, $[\alpha]_D$ –6.3° (*c* 0.49, MeOH), R_F 0.28 (S2), 0.53 (S3). FAB MS, *m/z* (rel.%): 414 (M + H, 80), 340 (77), 314 (100), 296 (20), 277 (33). IR (KBr): 1 454 (arom.); 1 603 (arom.), 1 700 (C=O, COOH dimer), 2 800 (OH, COOH dimer), 3 319 (OH, dimer), 3 424 (NH). ^{1}H NMR ($(CD_3)_2CO$): 1.31 s, 9 H ($(CH_3)_3C$); 1.64 ddd, 1 H, *J*(3a,2) = 3.5, *J*(3a,4) = 10.1, *J*(3a,3b) = 13.5 (H-3a); 1.98 ddd, 1 H, *J*(3b,4) = 2.5, *J*(3b,2) = 10.3, *J*(3a,3b) = 13.5 (H-3b); 2.71 dd, 1 H, *J*(6a,5) = 10.0, *J*(6a,6b) = 13.6 (H-6a); 2.83 dd, 1 H, *J*(6b,5) = 6.6, *J*(6a,6b) = 13.6 (H-6b); 2.99 dd, 1 H, *J*(11a,2) = 8.0, *J*(11a,11b) =

13.5 (H-11a); 3.05 dd, 1 H, *J*(11b,2) = 6.6, *J*(11a,11b) = 13.5 (H-11b); 3.07 dddd, 1 H, *J*(2,3a) = 3.5, *J*(2,11b) = 6.6, *J*(2,11a) = 8.0, *J*(2,3b) = 10.3 (H-2); 3.67 ddd, 1 H, *J*(4,3b) = 2.5, *J*(4,5) = 5.6, *J*(4,3a) = 10.1 (H-4); 3.76 dddd, 1 H, *J*(5,4) = 5.6, *J*(5,6b) = 6.6, *J*(5,NH) = 8.8, *J*(5,6a) = 10.0 (H-5); 5.83 bd, 1 H, *J*(NH,5) = 8.8 (NH); 7.13–7.30 m, 10 H (arom.). ^{13}C NMR ($(CD_3)_2CO$): 28.53 q ($(\mathbf{C}H_3)_3C$); 36.72 t (C-3); 36.90 t (C-11); 39.82 t (C-6); 44.52 d (C-2); 58.08 d (C-5); 72.59 d (C-4); 78.62 s ($(CH_3)_3\mathbf{C}$); 126.62 (arom.); 126.96 (arom.); 128.85 d (arom.); 129.05 d (arom.); 129.87 d (arom.); 130.18 d (arom.); 140.48 s (arom.); 140.58 s (arom.); 176.87 s (C-1). ($(CH_3)_3C\mathbf{O}C$=O) signal disappeared in the noise. For $C_{24}H_{31}NO_5$ (413.5) calculated: 69.71% C, 7.55% H, 3.38% N; found: 69.78% C, 7.69% H, 3.33% N.

(2*S*,4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoic Acid (**21**)

According to the general procedure, hydroxy acid **21** was obtained in 86% yield. Oil, R_F 0.28 (S2), 0.53 (S3). FAB MS, *m/z* (rel.%): 436 (M + Na, 10), 414 (M + H, 39), 358 (10), 340 (76), 314 (100), 296 (61), 120 (86). IR: 1 455 (arom.), 1 497 (amide II), 1 603 (arom.), 1 708 (C=O, COOH dimer), 1 767 (C=O, carbamate), 2 868 (OH, COOH dimer), 3 350 (OH, COOH dimer), 3 438 (NH), 3 500 (OH, COOH monomer), 3 622 (OH).

(2*R*,4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoic Acid (**20**)

According to the general procedure, hydroxy acid **20** was obtained in 95% yield. M.p. 122–125 °C, R_F 0.28 (S2), 0.53 (S3). FAB MS, *m/z* (rel.%): 414 (M + H, 12), 340 (24), 314 (31), 296 (20), 120 (29). IR: 1 455 (arom., 1 507 (amide II), 1 604 (arom.), 1 704 (carbamate and C=O, COOH dimer), 3 440 (NH).

(2*R*,4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoic Acid (**22**)

According to the general procedure, hydroxy acid **22** was obtained in 96% yield. M.p. 120–126 °C, R_F 0.28 (S2), 0.53 (S3). IR: 1 455 (arom.), 1 497 (amide II), 1 603 (arom.), 1 708 (C=O, carbamate), 1 767 (C=O, COOH monomer), 3 330 (OH, COOH dimer), 3 438 (NH), 3 500 (OH, COOH monomer).

(4*R*,5*S*)-4-Benzyl-5-{2-[(butylamino)carbonyl]ethyl}oxazolidin-2-one (**10**)

Lactone **8** (50 mg, 0.16 mmol) dissolved in butylamine (5 ml, 50 mmol) was warmed to 40 °C. When the lactone disappeared (8 h; TLC, S2), butylamine was evaporated, the residue was dissolved in ethyl acetate and washed with 10% citric acid, 10% $NaHCO_3$ and brine. The solution was dried ($MgSO_4$) and evaporated. The product, (4*R*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenylhexanoic acid *N*-butylamide (55 mg, 89%) was recrystallized from *t*-BuOMe–hexane, m.p. 154–157 °C. FAB MS, *m/z* (rel.%): 379 (M + 1, 19), 323 (8), 305 (5), 279 (49), 261 (6), 206 (6), 188 (15), 120 (24), 91 (67), 74 (53), 57 (100). IR: 1 455 (Ph), 1 504 (amide II), 1 603 (arom.), 1 653 (amide I), 1 700 (C=O, carbamate), 3 346 (OH, dimer), 3 444 (NH). For $C_{21}H_{34}N_2O_4$ (378.5) calculated: 66.63% C, 9.05% H, 7.40% N; found: 66.35% C, 9.12% H, 7.36% N.

Above-mentioned butylamide (38 mg, 0.1 mmol) was dissolved in dry DMF (5 ml), 60% suspension of sodium hydride in mineral oil (19 mg, 0.47 mmol) was added and the mixture was stirred for 3 h at room temperature. The suspension was then poured into saturated NaCl (14 ml) and the product was extracted with dichloromethane (3 × 10 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue, purified by preparative HPLC, afforded 22 mg (71%) of an oily product. FAB MS, *m/z* (rel.%): 327 (M + Na, 5), 305 (M + H,100), 188 (17), 146

(16), 128 (16), 91 (63), 74 (40), 57 (36). HR-FAB MS: for $C_{17}H_{24}N_2O_3$ calculated: 304.3924; found: 304.3723. ^{1}H NMR: 0.94 t, 3 H, *J*(10,9) = 7.3 (H-10); 1.36 m, 2 H (H-9); 1.50 m, 2 H (H-8); 2.03 dddd, 1 H, *J*(3a,2b) = 4.9, *J*(3a,2a) = 7.1, *J*(3a,4) = 11.2, *J*(3a,3b) = 14.1 (H-3a); 2.21 dddd, 1 H, *J*(3b,4) = 2.4, *J*(3b,2b) = 7.4, *J*(3b,2a) = 8.5, *J*(3a,3b) = 14.1 (H-3b); 2.37 ddd, 1 H, *J*(2a,3a) = 7.1, *J*(2a,3b) = 8.5, *J*(2a,2b) = 15.0 (H-2a); 2.49 ddd, 1 H, *J*(2b,3a) = 4.9, *J*(2b,3b) = 7.4, *J*(2a,2b) = 15.0 (H-2b); 2.66 dd, 1 H, *J*(6a,5) = 11.4, *J*(6a,6b) = 13.2 (H-6a); 2.92 dd, 1 H, *J*(6b,5) = 3.3, *J*(6a,6b) = 13.2 (H-6b); 3.27 m, 2 H, (H-7); 4.02 ddd, 1 H, *J*(5,6b) = 3.3, *J*(5,4) = 7.6, *J*(5,6a) = 11.4 (H-5); 4.71 dd, 1 H, *J*(4,3b) = 2.4, *J*(4,5) = 7.6, *J*(4,3a) = 11.2 (H-4); 4.84 bs, 1 H (NH); 5.61 bt, 1 H, *J*(NH,7) = 1.5 (NH); 7.16 m, 2 H (arom.); 7.29 m, 1 H (arom.); 7.35 m, 2 H (arom).

(4*S*,5*R*)-4-Benzyl-5-{(2*R*)-2-[(butylamino)carbonyl]-3-phenylpropyl}oxazolidine-2-one (**19**)

Oxazolidinone **19** was prepared from lactone **17** in a manner analogous to the preparation of oxazolidinone **10** in 50% yield. M.p. 126–128 °C (ether–hexane). FAB MS, *m/z* (rel.%): 395 (M + H, 100), 278 (8), 204 (6), 91 (100). HR-FAB MS: for $C_{24}H_{30}N_2O_3$ calculated: 394.5183; found: 395.5272 [M + H]. IR: 1 082, 1 232 (oxazolidinone ring), 1 455 (arom.), 1 522 (amide II), 1 604 (arom.), 1 666 (amide I), 1 759 (C=O, oxazolidinone), 3 446 (NH). ^{1}H NMR: 0.83 t, 3 H, *J*(10,9) = 7.3 (H-10); 1.07–1.17 m, 2 H (H-8); 1.21–1.29 m, 2 H (H-9); 1.98 ddd, 1 H, *J*(3a,4) = 2.9, *J*(3a,2) = 8.8, *J*(3a,3b) = 14.4 (H-3a); 2.22 ddd, 1 H, *J*(3b,2) = 4.2, *J*(3b,4) = 11.2, *J*(3a,3b) = 14.4 (H-3b); 2.57 dddd, 1 H, *J*(2,3a) = 4.2, *J*(2,11a) = 6.4, *J*(2,3a) = 8.8, *J*(2,11b) = 10.0 (H-2); 2.65 dd, 1 H, *J*(6a,5) = 3.7, *J*(6a,6b) = 13.4 (H-6a); 2.86 dd, 1 H, *J*(6b,5) = 11.2, *J*(6a,6b) = 13.4 (H-6b); 2.88 dd, 1 H, *J*(11a,2) = 10.0, *J*(11a,11b) = 13.2 (H-11a); 2.92 dd, 1 H, *J*(11b,2) = 6.4, *J*(11a,11b) = 13.2 (H-11b); 3.03 ddt, 1 H, *J*(7a,NH) = 5.6, *J*(7a,8a) = 7.1, *J*(7a,8b) = 7.1, *J*(7a,7b) = 14.2 (H-7a); 3.15 ddt, 1 H, *J*(7b,NH) = 6.2, *J*(7b,8a) = 6.6, *J*(7b,8b) = 6.6, *J*(7a,7b) = 14.2 (H-7b); 4.02 ddd, 1 H, *J*(5,6a) = 3.7, *J*(5,4) = 7.6, *J*(5,6b) = 11.2 (H-5); 4.82 ddd, 1 H, *J*(4,3a) = 2.9, *J*(4,5) = 7.6, *J*(4,3b) = 11.2 (H-4); 4.84 bs, 1 H (NH, oxazolidinone); 5.21 bt, 1 H, *J*(NH,7a) = 5.6, *J*(NH,7b) = 6.2 (NH); 7.13–7.37 m, 10 H (arom.). ^{13}C NMR: 13.64 q (C-10); 19.82 t (C-8); 31.32 t (C-9); 32.08 t (C-3); 36.27 t (C-11); 37.63 t (C-6); 39.08 t (C-7); 46.12 d (C-2); 56.80 d (C-5); 77.18 d (C-4); 126.57 d (arom.); 127.29 d (arom.); 128.54 d (arom.); 128.93 d (arom.); 128.93 d (arom.); 129.16 d (arom.); 136.43 s (arom.); 138.98 s (arom.); 158.03 s (C=O, oxazolidinone); 173.75 s (C-1).

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