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Synthesis and Conformational Features of Topographically Constrained Designer Chimeric Amino Acids: The β-Isopropyl Phenylalanines

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Abstract: All four optically pure isomers of the highly conformationally constrained novel chimeric amino acid, β-isopropylphenylalanine or β-phenylleucine, were asymmetrically synthesized in five to six steps in 20 -25% overall yield. Computer-assisted molecular modeling revealed that the β-isopropyl group in these chimeric amino acids plays the dominant role in determining the most favorable side chain conformations. © 1997 Elsevier Science Ltd.

INTRODUCTION

There is overwhelming evidence that the stereostructural properties of the side chain groups of amino acid residues in bioactive peptides are extremely important in peptide-receptor/acceptor recognition and bioactivity.[1,2] Therefore, in the rational design of peptides and non-peptide mimetics as potential drugs, it is crucial to understand not only the global bioactive conformation, but also the optimal orientation of functional side chain groups for receptor binding and signal transduction. The topographical approach has been developed in our laboratories using novel side chain constrained amino acids which were incorporated into polypeptide or non-peptide templates, to examine the side chain stereochemical requirements for binding of the peptides to their receptors and for signal transduction.[2a,c] Therefore, design and synthesis of novel amino acids with specifically constrained side chain groups has become extremely important for the design of highly selective and potent peptide hormone analogues using topographical considerations. However, in order to develop the general principles that are needed for the design of such topographically constrained novel amino acids, we need to carefully examine what kind of side chain orientations have the most promising possibilities for maximizing receptor recognition (binding) and biological transduction. Thus we sought to design novel topographically constrained amino acid analogues that would prefer only one or a very limited number of side chain conformers

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among those accessible for natural amino acid. We have applied these principles to design and synthesize a series of β–branched amino acids including β-methylphenylalanine, β-methyltyrosine, β-methyltryptophan, 2′,6′-dimethyl-β-methyltyrosine, and 2′,6′-dimethyl-β-methylphenylalanine, in which substitution of the diastereotropic β–hydrogens, and 2′,6′-hydrogens of natural aromatic α–amino acids provides an approach for the topographic control of side chain conformations.[3] Incorporation of these novel amino acids into bioactive peptide hormones and neurotransmitters has produced highly selective and potent peptide hormone analogues, and provided new insights into the stereochemical requirements of side chain groups in peptide-receptor interactions.[4] These studies showed also that developing new topographically constrained amino acids with more substantial restrictions of side chain mobility is crucial for future successful peptide design. Thus in this report we explore possibilities for introducing additional constraints in aromatic amino acid side chains by increasing the size and hydrophobility of substituents at the β-carbon atom, and present details of the asymmetric synthesis and conformational studies of a new member of the β-branched unusual amino acid family: β-isopropylphenylalanines (Figure 1). These chimeric amino acids contain two bulky side chain groups, isopropyl and phenyl. Therefore, it could be considered either as a phenylalanine derivative or a leucine derivative. The interaction between these two bulky side-chain groups can produce strong constraints simultaneously for both χ^1 and χ^2 torsional angles so that each diastereoisomer would favor a few low-energy side chain conformations separated by high energy barriers. Furthermore, the combination of phenyl and isopropyl groups also can provide significantly increased hydrophobic interactions with a receptor/acceptor. Thus, peptide ligands containing these unusual chimeric amino acids will possess unique physio-chemical and conformational properties, and provide useful information about the stereochemical requirements for peptide ligand-receptor interactions.

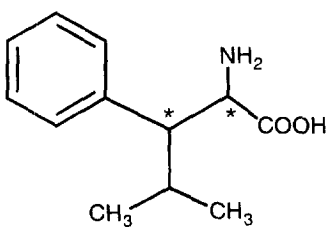
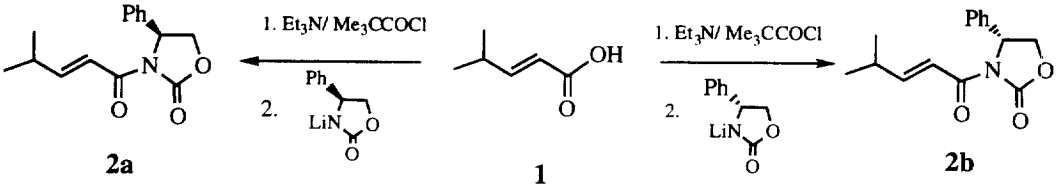


Figure 1. Structure of β-isopropylphenylalanines (* indicates the location of chiral centers).

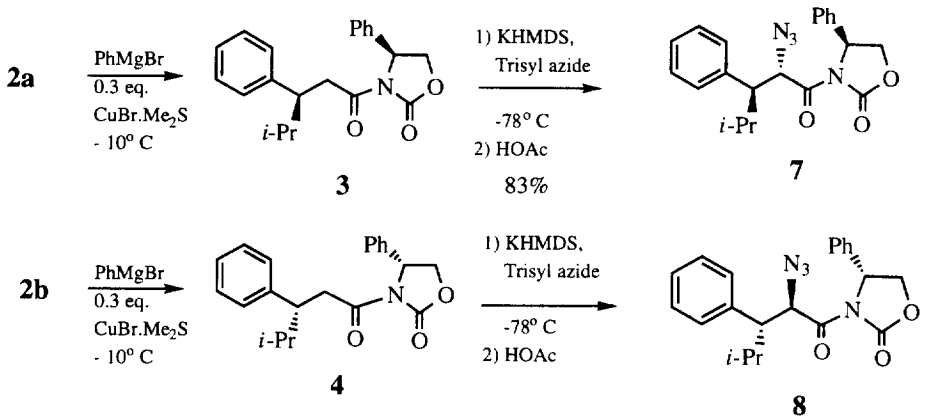
RESULTS AND DISCUSSION

Synthesis Two synthetic strategies were developed in these studies to furnish the novel β-substituted amino acids. One involved presetting of the stereochemistry at the β-position either by choice of starting materials or by chiral resolution of racemic β-phenylbutyric acid analogues via coupling with chiral reagents to provide optically pure diastereoisomers.[3a,f,i] In the other strategy, we introduced the use of optically pure 4-phenyloxazolidinones as chiral auxiliaries to induce a chiral center at the β-position of β-arylbutyric acids via asymmetric 1,4-additions to α,β-unsaturated acid derivatives with alkyl neucleophiles.[3b,d,g]

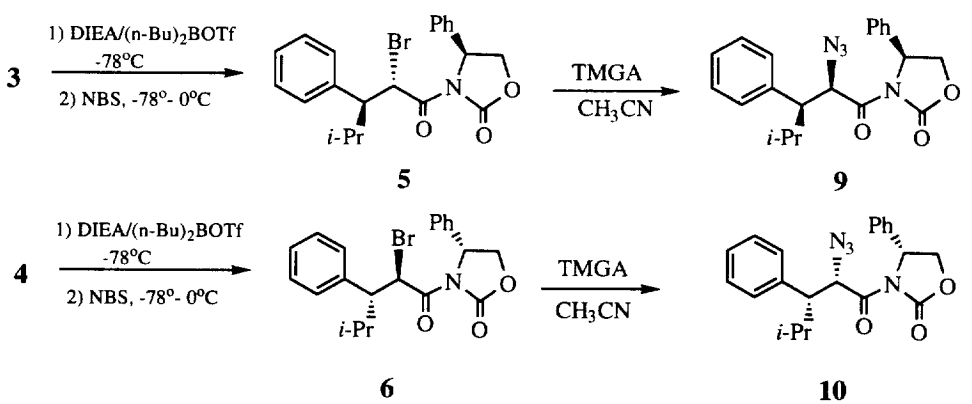
Scheme 1



Scheme 2



Scheme 3



Both approaches work well and provided sufficient optically pure stereoisomers of β-branched unusual amino acids for structural, conformational and dynamic studies, and for incorporation into peptides.[3,4]

In our initial attempt to synthesize the β-isopropylphenylalanines, 1,4-addition of an α,β–unsaturated chiral conjugate with isopropyl magnesium chloride did not work well under the reaction conditions reported previously from our laboratory.[3] Therefore, in our initial studies, the isopropyl group was preset at the β-position without regard to the chirality. Then optically pure (4R)- or (4S)-4-phenyl-oxazolidinone was used as a chiral resolution reagent, and simultaneously as a chiral auxiliary to provide the desired compounds.[5]

In the synthesis reported here, we started from isohexenoic acid **1** (Scheme 1), which was coupled with the optically pure (4S)- or (4R)-4-phenyloxazolidinones respectively to yield the (4S)- and (4R)-4-phenyl-3-isohexenyl-2-oxazolidinones **2a** and **2b** via the formation of the mixed anhydride with pivaloyl chloride (Scheme 1) in very good yield.[6] An asymmetric 1,4-addition to the chiral conjugate acceptor **2a** or **2b** produced β-phenyl isohexanoic acid derivatives **3** or **4**.[7] The direct azidation of **3** or **4** with trisyl azide at -78°C gave α-azido compounds **7** and **8** in 80-83% yield through the potassium imide-enolate direct azidation procedure (Scheme 2) as described by Evans and coworkers.[8] No diastereoisomers were detected in the crude azidation products around the α-proton resonance (~5.7 ppm) by ^{1}H NMR, which indicated that the α-azido groups were induced very stereoselectively in these constrained β-isopropyl substituted intermediates, and the *de* was estimated to be over 90%.

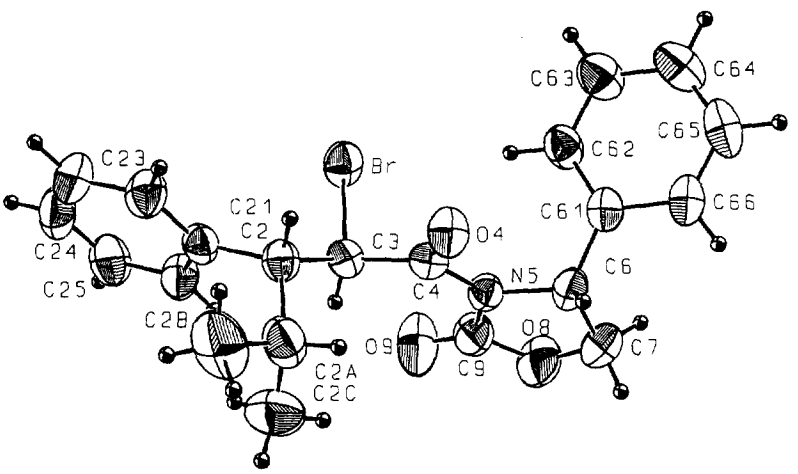
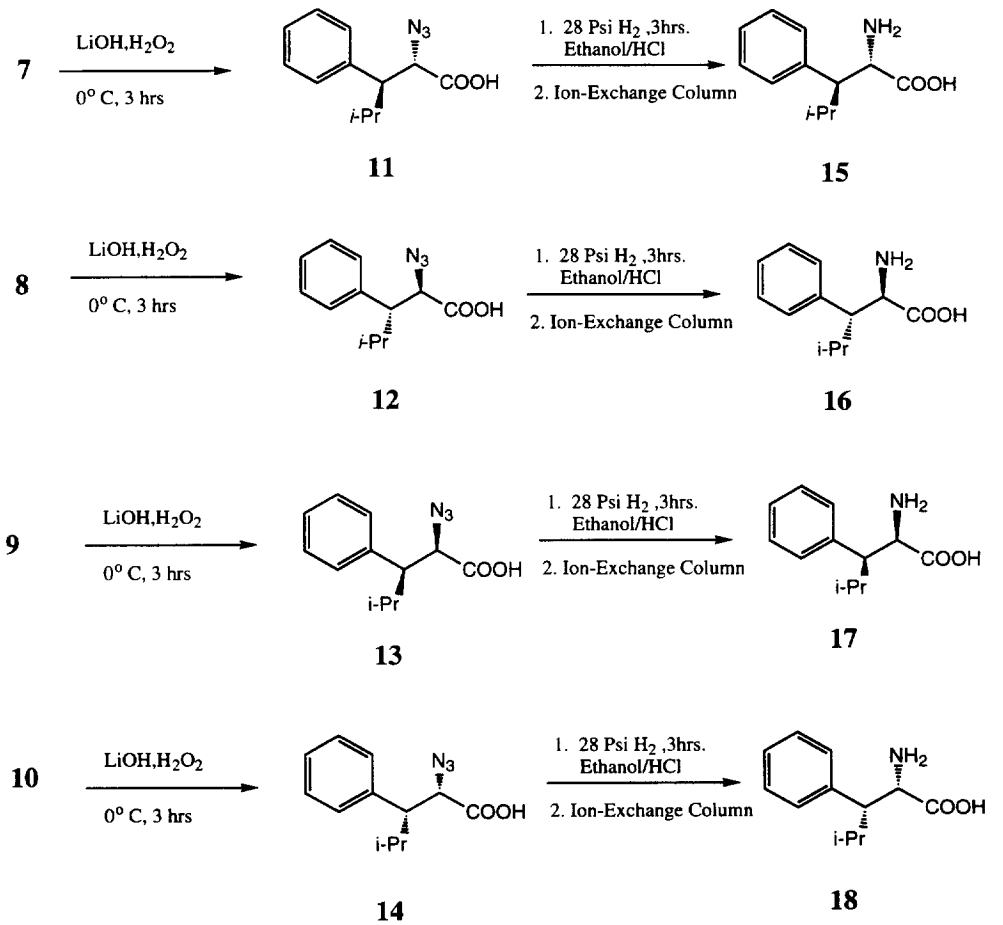


Figure 2. The X-ray crystal structure of (4R, 2′R, 3′R)-4-phenyl-3-[2′-bromo-3′-phenylisohexanyl)-2-oxazolidinone

Bromination of the boron enolate of **3** or **4** with NBS at -78°C produced α-bromo derivatives in over 85% yield,[3] and the *de* was estimated to be over 90% since no resonance signal from other diasteroisomers was observed at the resonance (around 6.3 ppm) of α-proton in the ^{1}H NMR of crude bromination products. The stereochemistry induced by the chiral auxiliary in the asymmetric 1,4-addition and bromination was confirmed

by an X-ray diffraction crystal structure of the brominated derivative, (4R,2′R,3′R)-4-phenyl-3-(2′-bromo-3′-phenylisohexanyl)-2-oxazolidinone **6** (Figure 2). Analysis on the crystal structure suggests that in the asymmetric 1,4-addition, the β-phenyl was added from re-face for **2a**, and from si-face for **2b**; in bromination reaction, the α-bromo group was induced from the si-face or re-face of boron enolate for **3** and for **4** respectively, presumably because the other face of the conjugates **2** or boron enolates was shielded by the phenyl ring of the oxazolidinone in the transition state of the 1,4-addition and bromination reactions.

Scheme 4



The α-bromo derivatives **5** and **6** were converted into the α-azido compounds **9** and **10** by treatment with tetramethylguanidine azide via an S_N2 mechanism.[3g] The non-destructive removal of the phenyloxazolidinone chiral auxiliary from the optical pure compounds, **7-10**, was accomplished by hydrolysis under basic conditions.[3] Hydrogenolysis of the α-azido acids **11-14** at 28 psi H_2 in the presence of 10% Palladium/carbon catalyst in methanol/HCl and subsequent purification by ion-exchange column chromatography (Scheme 4) gave the corresponding optically pure α-amino acids **15-18**. The diasteroisomeric purity of all β-isopropylphenylalanine isomers (*de*>95%) was determined by ^1H NMR spectroscopy and also by thin-layer chromatography on reverse-phase chiral silica gel plates.

Conformational Studies The side chain conformations of amino acids are defined by the set of torsional angles χ^1, χ^2, etc. In chimeric β-isopropylphenylalanine/β-phenyleucine, two side chain groups, phenyl and isopropyl, can act as important binding sites in ligand-receptor interactions. Therefore for a complete expression of the conformational features of the chimeric amino acids one needs to consider conformational profiles of both side chain groups. Based on the IUPAC nomenclature convention,[9] two sets of torsional angles for the chimeric side chains were defined as shown in Figure 3.

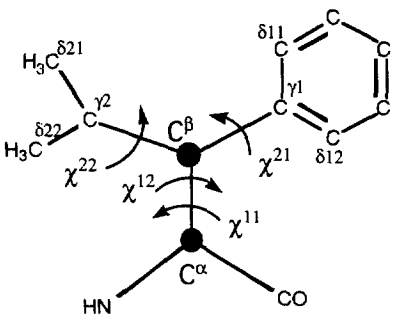


Figure 3. Definition of χ^{11}, χ^{12}, χ^{21}, χ^{22} in the Chimeric β–Isopropylphenylalanine/β–Phenylleucine

We define the higher-priority β-phenyl branch, as branch 1, and the lower-priority β-isopropyl branch, as branch 2. According to the IUPAC convention, the two γ-methyl carbons in branch 2 are numbered in a clockwise sense when viewed in the direction C^β -> $C^{\gamma 2}$, i.e. the *pro*-R carbon is defined as $C^{\delta 21}$ and the *pro*-S carbon is defined as $C^{\delta 22}$. The torsional angles χ^{11} (N-C^α-C^β-$C^{\gamma 1}$) and χ^{21} (C^α-C^β-$C^{\gamma 1}$-$C^{\delta 11}$) are used to define the side chain conformations of the chimeric amino acid as a phenylalanine derivative (β-iPrPhe), and the angles χ^{12} (N-C^α-C^β-$C^{\gamma 2}$) and χ^{22} (C^α-C^β-$C^{\gamma 2}$-$C^{\delta 21}$) are used to describe the side chain conformations in terms of a leucine derivative (β-PhLeu). Note that the angles χ^{11} and χ^{12} define a rotation about the same C^α-C^β bond, and hence, they are related as $\chi^{12} = \chi^{11} \pm 120°$ ("+" for 3R-isomers, "-" for 3S-isomers). In addition, according to the above definition, the χ^{22} angle always is counted to the pro-R $C^{\delta 21}$ atom without regardness of chirality. As a result, in mirror symmetrical conformations of *L*- and *D*-Leu, and of enantiomeric isomers of β-PhLeu, χ^{22}

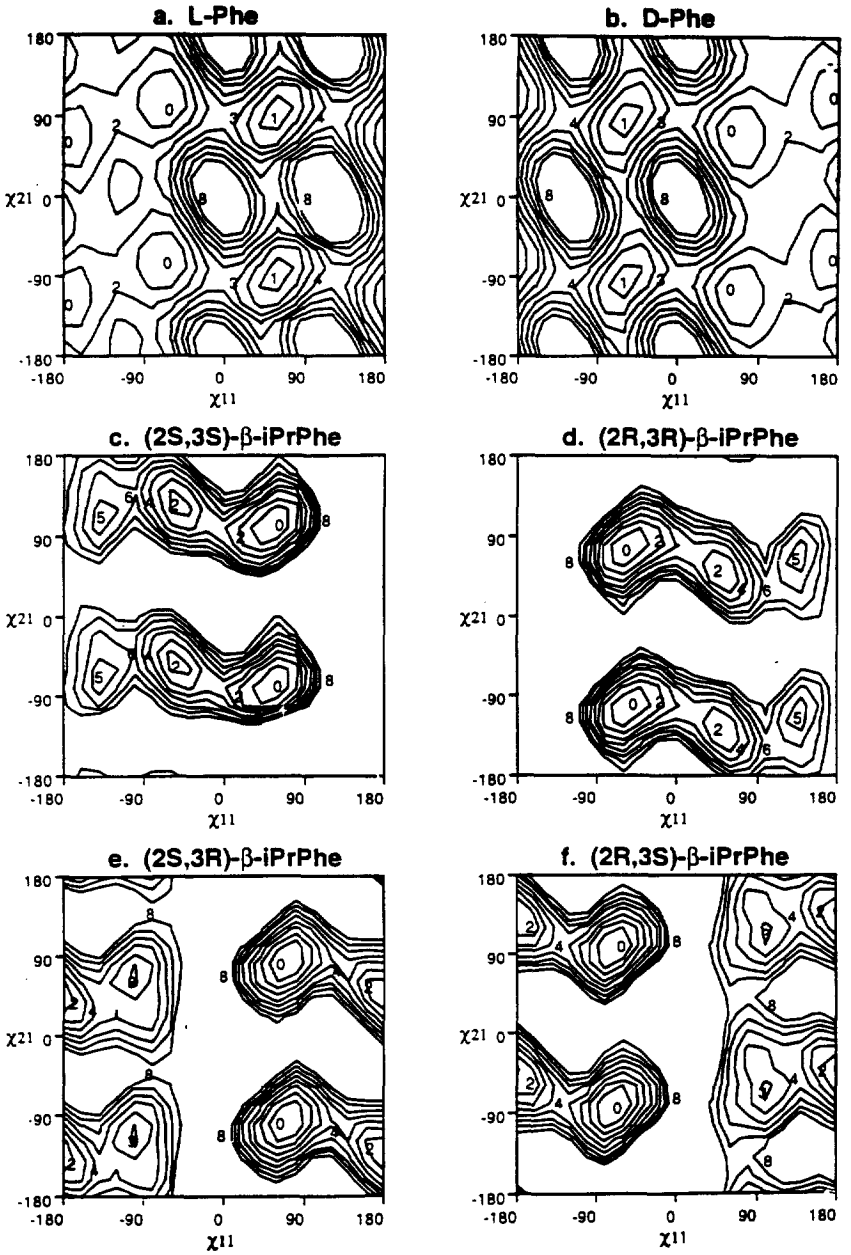


Figure 4. (χ^{11}, χ^{21}) Conformational energy map for Phe and β-iPrPhe. The energy contours are drawn at the intervals of 1 Kcal/mole.

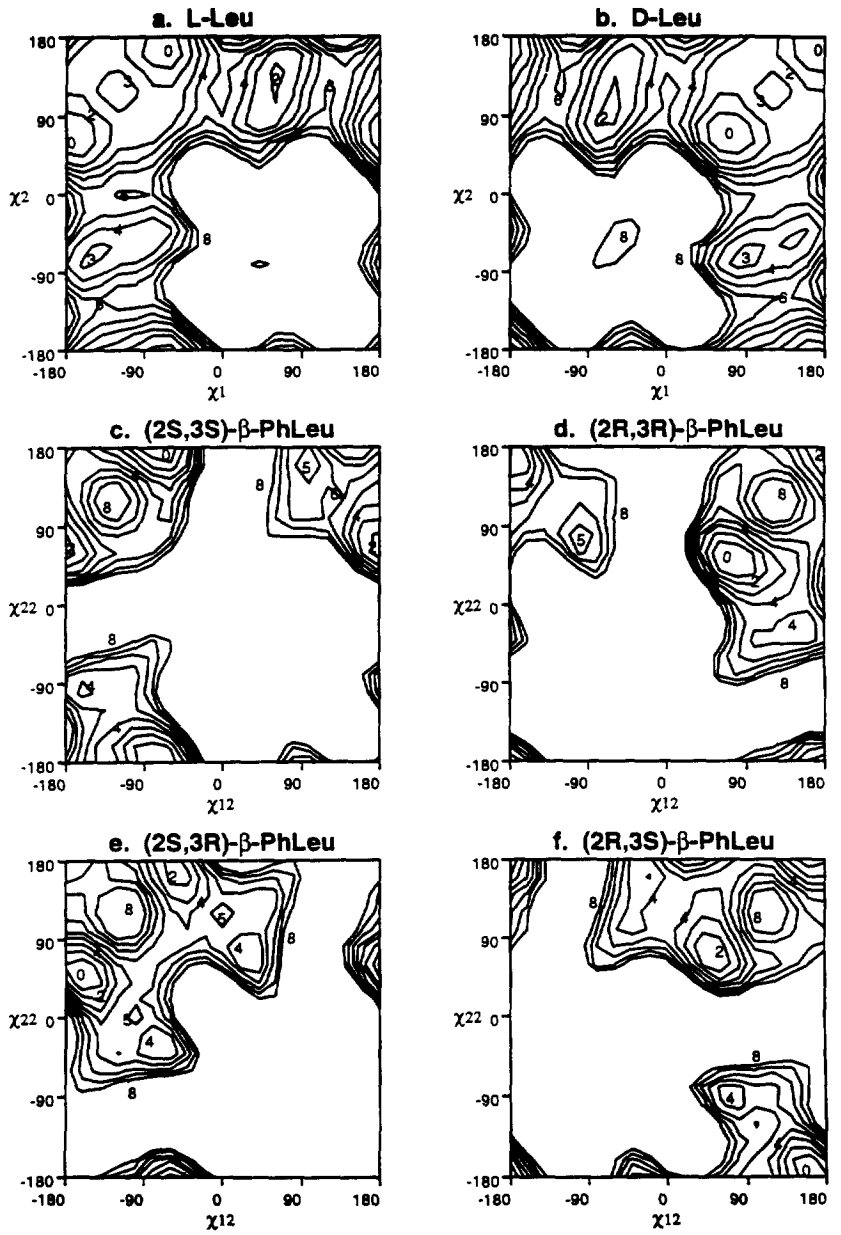


Figure 5. (χ^{12}, χ^{22}) Conformational energy map for Leu and β-PhLeu. The energy contours are drawn at the intervals of 1 Kcal/mole.

angles differ by ±120°. Therefore, the (χ^1, χ^2) maps for these enantiomers (see Figure 5) do not obey mirror image relationships.

The (χ^1, χ^2) energy maps for N^{α}-Acetyl-N-Methylamide derivatives of β-iPrPhe/β-PhLeu and that of the corresponding natural amino acids, *L,D*-Phe and *L,D*-Leu, are given in Figures 4 and 5, respectively. The conformational mobility of the phenylalanine side chain (Figure 5, **a** and **b**) is not highly restricted. High-energy regions ($\Delta E > 8$ kcal/mol) occupy only limited parts of the χ^1, χ^2 space, while low-energy regions ($\Delta E \leq 3$ kcal/mol) occupy about 50% of the map area. The energy minima corresponding to the three staggered χ^1 rotamers, *trans* ($\chi^1 = \pm 180°$), *gauche (+)* ($\chi^1 = 60°$) and *gauche (-)* ($\chi^1 = -60°$), are almost at the same energy level, and are separated by relatively low energy barriers (2 to 4 kcal/mol). The (χ^1, χ^2) space of the leucine side chain (Figure 6, **a** and **b**) is more restricted than that of phenylalanine. In particular, the *gauche (+)* χ^1 rotamer of *L*-Leu *(gauche (-)* χ^1 rotamer of *D*-Leu) is about 2 kcal/mole higher in energy than the two lowest energy rotamers.

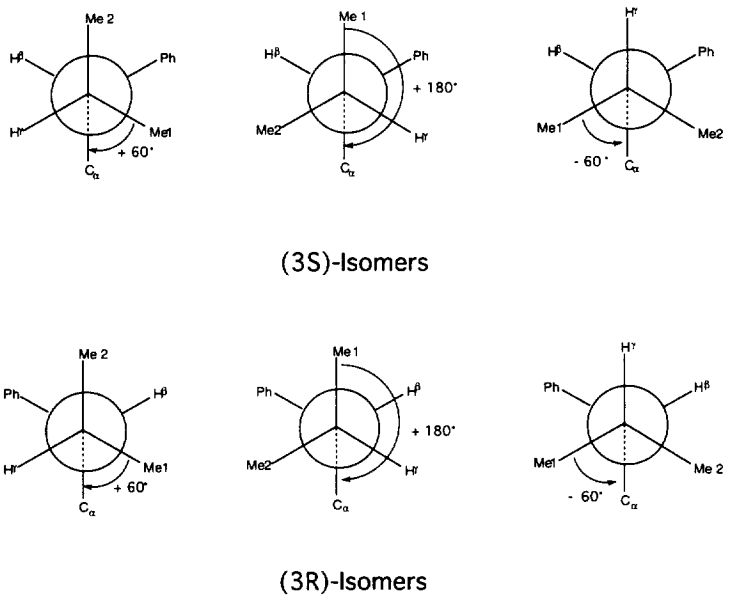


Figure 6. Newman projections of three staggered rotamers of χ^{22} for the pairs of β-phenylleucine isomers with the 3S (top) and 3R (bottom) configuration at the C^{β} atom (the C^{β}-C^{γ} bond is perpendicular to the plane of the projections)

The bulky β-phenyl substituent restricts considerably rotation about the χ^{22} torsional angle in β-PhLeu. This is illustrated in Figure 6 by Newman projections of the three staggered rotamers of χ^{22} for β-PhLeu isomers with the 3S and 3R configurations. Note that when a δ-methyl group is *gauche* to phenyl, unfavorable VDW contacts between one δ-methyl group and the phenyl group occurs, and a δ-methyl *gauche* to C^{α} causes unfavorable contacts with C^{α} and its nearest substituents. Therefore, the β-PhLeu side chain should prefer the χ^{22} rotamers that place one of the δ-methyl groups *trans* to phenyl and another one *trans* to C^{α}, thus minimizing the number of unfavorable VDW contacts, i.e. the rotamer with $\chi^{22} \approx \pm 180°$ for the 3S isomers and the rotamer

with $\chi^{22} \approx 60°$ for the 3R isomers. Indeed, these χ^{22} rotamers correspond to the global energy minima of the (χ^{12}, χ^{22}) maps for the respective isomers of β-PhLeu (Figure 5, **c** to **f**).

The β-isopropyl group greatly influences the χ^1 rotamer populations of β-PhLeu isomers. In particular, unfavorable interactions of the isopropyl group with the peptide backbone practically eliminates *gauche (+)* χ^{12} rotamers for the 2S-isomers and *gauche (-)* rotamers for the 2R-isomers. Corresponding energy minima of (χ^{12}, χ^{22}) maps in Figure 5, **c** to **f**, are 4-5 kcal/mol higher than the global minima, and they are displaced by ±30° from their usual positions at $\chi^1 = \pm 60°$. Note that according to the relation $\chi^{12} = \chi^{11} \pm 120°$, the *gauche (+)* χ^{12} rotamer of (2S,3S)- and (2S,3R)-β-PhLeu corresponds to the *trans* and *gauche (-)* χ^{11} rotamers of (2S,3S)- and (2S,3R)-β-iPrPhe, respectively, which become the highest-energy rotamers of the phenyl branch of the chimeric amino acids (see Figure 4, **c** and **e**). Similarly, the *trans* χ^{11} rotamer of (2R,3R)-β-iPrPhe and the *gauche (+)* rotamer of (2R,3S)-β-iPrPhe (Figure 4, **d** and **f**) are discriminated due to the unfavorable *gauche (-)* conformation of the β-isopropyl group in these *D*-amino acid isomers of β-PhLeu. These results were further supported by the NMR-based side chain conformational studies of opioid peptide analogues of [β-iPrPhe^3]Deltorphin I.[10]

The *gauche (-)* χ^{12} rotamer of the (2S,3S)-isomer and the *trans* χ^{12} rotamer of the (2S,3R)-isomer allow the optimal favorable interaction of the β-isopropyl group both with the backbone and with phenyl ring and, therefore, they correspond to the global energy minima of the two isomers of β-PhLeu. Note now that the *gauche (-)* rotamer of (2S,3S)-PhLeu and the *trans* rotamer of (2S,3R)-PhLeu both correspond to the *gauche (+)* rotamer of the corresponding (2S,3S)-iPrPhe and (2S,3R)-iPrPhe isomers. Thus, because of the steric preferences of the β-isopropyl group, the *gauche (+)* χ^{11} rotamer becomes the lowest-energy side chain conformation of (2S,3S)- and (2S,3R)-β-iPrPhe. The same is true for the (2R,3R)- and (2R,3S)-isomer, with the only difference being that for the *D*-amino acids the *gauche (-)* χ^{11} rotamer is the most favorable one. However, we should be very cautious here since the energy difference between the two low energy χ^{11} or χ^{12} rotamers is only about 2 kcal/mole, and this is not large enough to make general conclusions. The actual populations of these two rotamers in a polypeptide will depend on the preferred backbone conformation and on the environment.[10]

Conclusions. Four diastereoisomers of the novel chimeric amino acids β-isopropylphenylalanine have been synthesized asymmetrically with high optical purity in an efficient manner. Molecular modeling of the chimeric β-iPrPhe/β-PhLeu amino acids has shown that the β-substituted phenyl group does not change dramatically the conformational properties of the leucine side chains. Its influence eliminates the least populated *gauche (+)* rotamer of *L*-Leu and the *gauche (-)* rotamer of *D*-Leu, and stabilizes a *gauche (-)* conformation of the leucine branch in (2S,3S)-PhLeu, a *gauche (+)* conformation in (2R,3R)-PhLeu, and a *trans* conformation in (2S,3R)- and (2R,3S)-PhLeu. The β-substituted isopropyl group strongly affects the phenyl group and biases conformational preferences of the phenylalanine side chain. Its influence discriminates one of two lowest-energy rotamers of *L*- and *D*-Phe and stabilizes the least populated conformations of the natural side chain, i.e. the *gauche (+)* rotamer for both 2S-isomers and the *gauche (-)* rotamer for both 2R-isomers. Thus, substitution of Phe with the chimeric β-iPrPhe amino acids can bias considerably the topographical properties of bioactive peptides and modulate the profiles of their biological activities. Incorporation of this unusual chimeric amino acids into peptide hormone Deltorphin I has produced interesting results, the detailed structure-activity

relationship and NMR-based conformational studies of [β-iPrPhe[3]]Deltorphin I will be published separately soon.[10]

Experimental

General. All reagents, unless otherwise noted, were purchased from Aldrich Chemical Co. and were used without further purification. Triisopropylsulfonyl azide and tetramethyl guanidine azide were synthesized as described in the literature.[11] The following solvents were freshly distilled and stored under argon prior to use: THF from Na/benzophenone ketyl, CH_2Cl_2 from CaH_2. Water was distilled and deionized before use. All reactions, unless otherwise noted were carried out under the protection of argon; the reaction temperatures listed are the bath temperatures. All reaction containers were flame dried under vacuum before use. All melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 250 (operating at 250.0 and 62.9 M Hz) spectrometer, using tetramethylsilane (TMS) or D_2O (4.66 ppm down field from TMS) as internal standard, or CDCl3 (77.0 ppm downfield from TMS) as internal standard for ^{13}C NMR. Optical rotations were taken on an Autopol III polarimeter using a 1.0 dm cell. Flash column chromatography was performed using EM silica gel. Solvents for chromatography were used without further purification. Analytical tlc was performed on Merck precoated Kieselgel 60 F-254 plates with the following solvent systems(v/v): (**I**) EtOAc/hexanes (3/7); (**II**) EtOAc/hexanes/HOAc(30/70/1); (**III**) $CH_3CN/CH_3OH/H_2O$(4/1/1). Chiralplate® reverse phase silica gel impregnated with a chiral selector and Copper (II) ions (Machery Nagel Co. FGR). The separation of optical isomers is based on ligand exchange. Products were detected using either I_2, ninhydrin, or UV light. A jacked column with the inside diameter of 25 mm and length of 450 mm purchased from ACE glass was used for ion-exchange column chromatography. Elemental analysis was done by Desert Analytics Co., Tucson, Arizona. High resolution mass spectra were obtained from the Mass Spectroscopy Service Laboratory, Department of Chemistry, The University of Minnesota, Minneapolis, and the Mass Spectroscopy Laboratory, Department of Chemistry, The University of Arizona, Tucson.

Molecular Modeling Methods for Calculations. The (χ^1, χ^2) energy maps for AcNH-(*D,L*)-Phe-CO-NHME, AcNH-(*D,L*)-Leu-CO-NHME and stereoisomers of AcNH-β-iPrPhe-CO-NHME were calculated using the united-atom OPLS* force field[12] implemented in the Macromodel program[13] (version 4.5). The model dipeptides with blocked amino and carboxyl groups were chosen in order to mimic incorporation of these residues into a peptide chain. A dielectric constant $\varepsilon = 4.0$ was used to reproduce experimental characteristics of peptides.

The (χ^1, χ^2) energy maps were calculated with 20° steps in each direction within the intervals from -180° to 180° using the *Drive* procedure implemented in Macromodel 4.5. We first calculated a series of "conditional" (χ^1, χ^2) maps for each compound with the backbone constrained in a particular low-energy region of the (φ,ψ) space by penalty potentials $U_{const} = U_0 \cos(\theta-\theta_0)$ applied when a torsional angle θ deviates from a specified interval $\theta_0 \pm \Delta\theta$. We then merged the "conditional" maps into a "cumulative" map, selecting at each grid point the lowest energy value from those obtained in all conditional maps. This procedure insures that the final maps

represent the (χ^1, χ^2) space with an optimal backbone conformation at each grid point. Contours of equal relative energies, $\Delta E = E-E_{min}$ of the maps in Figures 4 and 5 were drawn with the step of 1.0 kcal/mol from 1.0 to 8.0 kcal/mol using the *Plt2D* module of Macromodel 4.5.

General Procedure to Synthesize 3-(2′-Isohexenyl)-4-phenyl-2-oxazolidone: Into a three-neck flask with magnetic stirring bar was placed (*E*)-2-Isohexanoic acid (2.50 g, 21.9 mmol) prepared by published procedures[14] and THF (124 mL). After the solution was cooled to -78°C for 15 min, triethylamine (3.7 mL, 24.3 mmol) was added via syringe followed by trimethylacetyl chloride (3.0 mL, 24.1 mmol). The resulting white suspension was stirred at -78°C for 15 min, 0°C for one hour, and then at -78°C for 15 min before transferring via cannula into a light yellow slurry of lithiated 4(S)-4-phenyl-2-oxazolidinone at -78°C, prepared 10 min in advance at -78°C by addition of n-butylithium (15 mL of a 1.6 M solution in hexane) into the solution of (4S)-4-phenyl-2-oxazolidinone (3.91 g, 24 mmol) in THF (74 mL) at -78°C. The resulting slurry was stirred at -78°C for 15 min, then four hours at room temperature. The reaction was quenched with 80 mL saturated ammonium chloride. The volatiles were removed by rotary evaporation, the residue was diluted by addition of 50 mL water, and then extracted with dichloromethane(3 x 80 mL). Evaporation of the dried organic extracts over anhydrous magnesium sulfate left an yellow oil. The crude product was purified by flash silica gel chromatography using 1:9 EtOAc:hexane mixtures as eluent.

(4S,2*E*)-3-(2′-Isohexenyl)-4-phenyl-2-oxazolidinone 2a: White solid (83%), mp:103.0-104.0 °C, R_f=0.44 (**II**), $[\alpha]^{20}_D$=+103.1° (c=1.0, $CHCl_3$). ^{1}H NMR δ ppm: 7.39-7.28(m, 5H, aromatic protons), 7.20(dd, J=16.4, 0.8Hz, 1H, -CH=C-), 7.03(dd, J=16.4, 6.5Hz, -C=CH-), 5.46(dd, J=8.7, 3.8Hz, 1H, oxazolidinone, PhCH-), 4.67(t, 1H, J=8.7 Hz, oxazolidinone, -CH_2-*/proR*), 4.25 (dd, J=8.7, 3.8Hz, 1H, oxazolidinone, -CH_2-*/proS*), 2.49[m, 1H, , -$CH(CH_3)_2$], 1.04[dd, J=6.8, 6H, -$CH(CH_3)_2$]. ^{13}C NMR δ ppm: 164.9, 158.1, 153.7, 139.1, 129.3, 128.5, 125.7, 117.6, 70.4, 57.2, 31.7, 21.4, 21.3. IR (KBr, cm^{-1}): 3037, 2963, 2917, 1774, 1682, 1635, 1393, 1353, 1213, 981, 713. Elemental Anal. for $C_{15}H_{17}O_3N$, Calcd.%: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.46; H, 6.57; N, 5.53.

(4R,2*E*)-3-(2′-Isohexenyl)-4-phenyl-2-oxazolidinone 2b: White solid (85%), mp:103.5-104.0 °C, $[\alpha]^{20}_D$=-103.4° (c=1.0, $CHCl_3$), R_f=0.43(**II**). ^{1}H NMR: δ ppm: 7.39-7.28(m, 5H, aromatic protons), 7.20(dd, J=16.4, 0.8Hz, 1H, -CH=C-), 7.03(dd, J=16.4, 6.5Hz, -C=CH-), 5.46(dd, J=8.7, 3.8Hz, 1H, oxazolidinone PhCH-), 4.67(t, 1H, J=8.7 Hz, oxazolidinone, -CH_2-*/proR*), 4.25 (dd, J=8.7, 3.8Hz, 1H, oxazolidinone, -CH_2-*/proS*), 2.49[m, 1H, , -$CH(CH_3)_2$], 1.04[dd, J=6.7, -$CH(CH_3)_2$]. ^{13}C NMR δ ppm: 164.9, 158.0, 153.7, 139.1, 129.1, 128.0, 125.9, 117.6, 69.8, 57.7, 31.4, 21.2, 21.1. IR (KBr, cm^{-1}): 3037, 2964, 2915, 1774, 1683, 1636, 1394, 1361, 1212, 980, 712. Elemental Anal. for $C_{15}H_{18}O_3N$, Calcd.%: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.64; H, 6.57; N, 5.36.

General Procedure for Synthesis of 3-(3′-Phenylisohexanyl)-4-phenyl-2-oxazolidinone: To a mixture of PhMgBr (1.7 mmol, 1.5 equivalents) and CuBr·SMe_2 (36 mg, 0.15 equivalents) in 5 mL THF at -20°C was added dropwise a solution of (4S,2*E*)-3-(2′-isohexenyl)-4-phenyl-2-oxazolidinone (1.16 mmol, 1.0 equivalent) in 3 mL of freshly distilled THF. A yellow color was observed during the addition process. The resulting mixture was kept stirring at -15°C for two hours, then slowly warmed to room temperature during one hour. The reaction was then quenched with 20 mL of saturated ammonium chloride, and the product was

extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), water (20 mL), and dried over anhydrous magnesium sulfate. After evaporation of the dried organic phases, the crude product was purified by silica gel chromatography.

(4S,3′S)-3-(3′-Phenylisohexanyl)-4-phenyl-2-oxazolidinone (3): White solid (84%), mp: 102.0-103.5°C, R_f=0.49 (**I**), $[\alpha]^{20}_D$=+57.1° (c=1.0, $CHCl_3$). ^1H NMR: δ ppm: 7.25-6.77ppm(m, 10H, aromatic protons), 5.29(dd, J=8.7, 4.1Hz, 1H, oxazolidinone Ph-CH-), 4.56(t, 1H, J=8.7 Hz, oxazolidinone, -CH_2-*/proR*), 4.07 (dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -CH_2-*/proS*), 3.74(dd, J=15.7, 10Hz, 1H, -C_αH-), 3.13(dd, J=15.7, 5.2Hz, 1H, -C_αH-), 2.95(m, 1H, -C_βH-), 2.88(m, 1H, , -$CH(CH_3)_2$), 0.96(d, J=6.7Hz, 3H, -CH_3), 0.74(d, J=6.7Hz, 3H, -CH_3). ^{13}C NMR: δ ppm 172.1, 153.7, 142.5, 138.4, 129.0, 128.5, 128.1, 128.0, 126.2, 125.1, 69.8, 57.5, 48.8, 38.2, 33.3, 20.7, 20.4. IR (KBr, cm^{-1}): 3027, 2950, 2868, 1788, 1702, 1392, 1364, 1187, 1072, 857. Elemental Anal. for $C_{21}H_{23}O_3N$, Calcd.%: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.61; H, 6.93; N, 4.22.

(4R,3′R)-3-(3′-Phenylisohexanyl)-4-phenyl-2-oxazolidinone (4): White solid (80%), mp: 102.0-103.5°C, R_f=0.48(**I**), $[\alpha]^{20}_D$= -54.6° (c=1.0, $CHCl_3$). ^1H NMR: δ ppm: 7.25-6.77ppm (m, 10H, aromatic protons), 5.29(dd, J=8.7, 4.1Hz, 1H, oxazolidinone Ph-CH-), 4.56(t, 1H, J=8.7 Hz, oxazolidinone, -CH_2-*/proR*), 4.07 (dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -CH_2-*/proS*), 3.74(dd, J=15.7, 10Hz, 1H, -C_αH-), 3.13(dd, J=15.7, 5.2Hz, 1H, -C_αH-), 2.95(m, 1H, -C_βH-), 2.88(m, 1H, -$CH(CH_3)_2$), 0.96(d, J=6.7Hz, 3H, -CH_3), 0.74(d, J=6.7Hz, 3H, -CH_3). ^{13}C NMR: δ ppm 171.8, 153.7, 142.9, 129.0, 128.5, 128.4, 128.0, 126.2, 125.9, 125.1, 69.8, 57.5, 48.4, 38.9, 33.2, 20.7, 20.5. IR (KBr, cm^{-1}): 3027, 2951, 2869, 1788, 1702, 1391, 1364, 1188, 1073, 858. Elemental Anal. for $C_{21}H_{23}O_3N$, Calcd.%: C, 74.75; H, 6.87; N, 4.15. Found: C,74.34; H, 6.97; N, 4.34.

General Procedures for Direct Azidation. A typical procedure is illustrated by the preparation of (4S,2′S,3′S)-3-(2′-azido-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone: To 40 mL of dry THF stirred at -78° C under Ar was added 28 mL of KHMDS (0.5 M in toluene, 14.0 mmol, 1.1 equivalent). To the resulting solution was added via cannula a precooled solution of (4S,3′S)-3-(3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (4.3 g, 12.7 mmol) in 54 mL of freshly distilled THF at -78°C. The resulting yellow solution was kept stirring at -78°C for another 30 min. To the above stirred solution of potassium enolate at -78°C was added via cannula a precooled solution of trisyl azide (4.5 g, 14.5 mmol, 1.14 equivalents) in 50 mL of THF at -78°C. After 2 min, the reaction was quenched with AcOH (3.4 mL, 58.4 mmoles, 4.6 equivalents). The reaction flask was immediately immersed into a water bath at 28°C for 35 min with stirring, and the reaction was monitored by TLC. Then, 150 mL ether was added, followed by 100 mL of dilute sodium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether (3 x 80 mL). The combined organic phases were dried over anhydrous magnesium sulfate and evaporation of the dried solution gave a light yellow oil. The crude product was further purified by silica gel column chromatography with a 1:9 ethyl acetate/hexanes mixture.

(4S,2′S,3′S)-3-(2′-Azido-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (7): Colorless oil (85%), R_f=0.48(**I**), $[\alpha]^{20}_D$= -52.46° (c=1.0, $CHCl_3$). ^1H NMR: δ ppm 7.34-7.18(m, 10H, aromatic protons), 5.70(d, J=7.1Hz, 1H, -C_αH-), 5.18(dd, J=8.4, 3.1Hz, oxazolidinone Ph-CH-), 4.68(t, J=8.3Hz, 1H, oxazolidinone, -CH_2-*/proS*), 4.27(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*/proR*), 3.02(dd, J=7.5Hz,

1H, -C_βH-), 2.10[m, 1H, -CH(CH_3)$_2$], 1.04(d, J=6.6 Hz, 3H, -CH_3), 0.75(d, J=6.6 Hz, 3H, -CH_3). IR (film): 3029, 2952, 2102, 1746, 1698, 1387, 1372, 704. MS for $C_{21}H_{22}O_3N_4$, Calcd. 378.1692 (M^+), Found: 379.1771 (M^++H).

(4R,2′R,3′R)-3-[2′-Azido-3′-phenylisohexanyl]-4-phenyl-2-oxazolidinone (8): Colorless oil (73%), R_f=0.49(**I**). $[\alpha]^{20}_D$= +48.9° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.34-7.18(m, 10H, aromatic protons), 5.70(d, J=7.1Hz, 1H, -C_αH-), 5.18(dd, J=8.4, 3.1Hz, oxazolidinone Ph-CH-), 4.68(t, J=8.3Hz, 1H, oxazolidinone, -CH_2-*proS*), 4.27(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*proR*), 3.02(dd, J=7.5Hz, 1H, -C_βH-), 2.10[m, 1H, -CH(CH_3)$_2$], 1.04(d, J=6.6 Hz, 3H, -CH_3), 0.75(d, J=6.6 Hz, 3H, -CH_3). IR (film): 3030, 2953, 2926, 2103, 1763, 1699, 1388, 1372, 1212, 703. MS for $C_{21}H_{22}O_3N_4$, Calcd. 378.1692 (M^+); Found: 379.1770 (M^++H).

General Procedures For Bromination: Into a solution of 3-(3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (8.15 mmol, 1.0 equivalent) in 60 mL of freshly distilled methylene chloride at -78°C was added diisopropylethylamine (1.6 mL, 9.8 mmol) and then dibutylboron triflate (9.0 mL, 1.0 M, 9.0 mmol) was added to the stirred solution via a syringe. The clear solution was stirred at -78°C for 15 min, 0°C for one hour (the solution turned deeper yellow), and recooled to -78°C for 15 min before transferring via cannula to a stirred slurry of NBS (2.9 g, 16.3 mmol) in dichloromethane (40 mL) at -78°C. The resulting purple solution was stirred at -78°C for one hour (the solution turned deep purple), and at 0°C (ice-bath) for 3 hours. The reaction was quenched by addition of 0.5 N sodium bisulfate (60 mL). The aqueous and organic solutions were separated, and the aqueous phase was extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with 0.5 N sodium thiosulfate(3 x 80 mL), water(2 x 100 mL), and dried over anhydrous $MgSO_4$. Evaporation of the dried solution left the crude product, which was further purified by flash column chromatography.

(4S,2′S,3′S)-3-(2′-Bromo-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (5): White solid (82%), mp:157.5-158.5°C, R_f=0.49(**I**), $[\alpha]^{20}_D$= -10.4° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.36-7.16(m, 10H, aromatic protons), 6.33(d, J=11.2Hz, 1H, -C_αH-), 5.47(dd, J=8.9, 4.7 Hz, 1H, oxazolidinone Ph-CH-), 4.75 (t, J=8.8Hz, 1H, oxazolidinone, -CH_2-*proS*), 4.28(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*proR*), 3.37(dd, J=10.8, 4.5Hz, 1H, -C_βH-), 2.02[m, 1H, -CH(CH_3)$_2$], 0.84(d, J=6.7 Hz, 3H, -CH_3), 0.78(d, J=6.7 Hz, 3H, -CH_3)). ^{13}C NMR: δ ppm 168.1, 152.9, 137.8, 137.5, 129.6, 129.1, 128.9, 127.7, 127.0, 125.9, 69.9, 58.0, 53.3, 46.7, 30.6, 22.1, 17.5; IR (KBr, cm^{-1}): 3038, 2960, 2923, 1774, 1702, 1386, 1366, 1206, 1064, 706. Elemental Anal. for $C_{21}H_{22}O_3NBr$, Calcd.%: C, 60.71, H, 5.34, N, 3.37; Found: C, 60.56, H, 5.36, N, 3.33.

(4R,2′R,3′R)-3-(2′-Bromo-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (6): White solid (80%), mp:158-159°C, R_f=0.47(**I**), $[\alpha]^{20}_D$= +7.20° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.36-7.16(m, 10H, aromatic protons), 6.33(d, J=11.2Hz, 1H, -C_αH-), 5.47(dd, J=8.9, 4.7 Hz, 1H, oxazolidinone Ph-CH-), 4.75 (t, J=8.8Hz, 1H, oxazolidinone, -CH_2-*proS*), 4.28(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*proR*), 3.37(dd, J=10.8, 4.5Hz, 1H, -C_βH-), 2.02[m, 1H, -CH(CH_3)$_2$], 0.84(d, J=6.7 Hz, 3H, -CH_3), 0.78(d, J=6.7 Hz, 3H, -CH_3). ^{13}C NMR: δ ppm 168.1, 152.9, 137.8, 137.5, 129.6, 129.1, 128.9, 127.7, 127.0, 125.9, 69.9, 58.0, 53.3, 46.7, 30.6, 22.1, 17.5; IR (KBr, cm^{-1}): 3039, 2960, 2922, 1775, 1702, 1386, 1366, 1205,

1065, 706. Elemental Anal. for $C_{21}H_{22}O_3NBr$, Calcd.%: C, 60.71, H, 5.34, N, 3.37. Found: C, 60.56, H, 5.36, N, 3.33.

General Procedures For Azide Displacement. A mixture of 3-(2′-bromo-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (6.0 mmol, 1.0 equivalent), tetramethylguanidine azide (9 mmol, 1.5 equivalents) in 50 mL acetonitrile was stirred under Ar at room temperature for 24 hours. TLC indicated that the reaction was complete. The solid was filtered off, and the filtrate was evaporated to dryness. The crude product was purifed by flash silica gel chromatography.

(4S,2′R,3′S)-3-(2′-Azido-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (9): White solid (78%), mp: 151-152°C. R_f= 0.62(I), $[\alpha]^{20}_D$= +54.4° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.37-6.44(m, 10H, aromatic protons), 5.76(d, J=11.5 Hz, 1H, -C_αH-), 5.30(dd, J=8.9, 4.7Hz, 1H, oxazolidinone Ph-CH-), 4.68(t, J=8.8Hz, 1H, oxazolidinone, -CH_2-*proS*), 4.03(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*proR*), 3.13(dd, J=4.1, 4.0 Hz, 1H, -C_βH-), 2.10[m, 1H, -$CH(CH_3)_2$], 0.92(d, J=6.8 Hz, 3H, -CH_3), 0.82(d, J=6.8 Hz, 3H, -CH_3). ^{13}C NMR: δ ppm 169.6, 153.1, 137.3, 136.0, 129.8, 129.0, 128.2, 128.0, 127.2, 124.8, 69.8, 58.6, 57.6, 52.1, 28.5, 21.1, 17.1. IR (KBr, cm^{-1}): 3029, 2952, 2925, 2102, 1764, 1698, 1387, 1370, 1212, 703. MS for $C_{21}H_{22}O_3N_4$, Calcd. 378.1692 (M^+); Found: 379.1778 (M^++H).

(4R,2′S,3′R)-3-(2′-Azido-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (10): White solid (80%), mp: 149-151°C, R_f= 0.64(I), $[\alpha]^{20}_D$= -43.2° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 7.37-6.44(m, 10H, aromatic protons), 5.76(d, J=11.5, 1H, -C_αH-), 5.30(dd, J=8.9, 4.7Hz, oxazolidinone Ph-CH-), 4.68(t, J=8.8Hz, 1H, oxazolidinone, -CH_2-*proS*), 4.03(dd, J=8.9, 4.7Hz, 1H, oxazolidinone, -CH_2-*proR*), 3.13(dd, J=4.1, 4.0 Hz, 1H, -C_βH-), 2.10[m, 1H, -$CH(CH_3)_2$], 0.92(d, J=6.8 Hz, 3H, -CH_3), 0.82(d, J=6.8 Hz, 3H, -CH_3), ^{13}C NMR: δ ppm 169.6, 153.1, 137.3, 136.0, 129.8, 129.0, 128.2, 128.0, 127.2, 124.8, 69.8, 58.6, 57.6, 52.1, 28.5, 21.1, 17.1. IR (KBr, cm^{-1}): 3030, 2953, 2926, 2103, 1763, 1699, 1388, 1371, 1213, 703. Elemental Anal. for $C_{21}H_{22}O_3N_4$, Calcd.%: C, 66.64, H, 5.86, N, 14.81; Found: C, 66.61, H, 5.68, N, 14.66.

General Procedures for the Hydrolysis of 3-(2′-Azido-3′-Phenylisohexanyl)-4-phenyl-2-oxazolidinone. Illustrated by the preparation of (2R,3R)-2-azido-3-phenylisohexanoic acid. To a solution of 3-(2′-bromo-3′-phenylisohexanyl)-4-phenyl-2-oxazolidinone (2.2 g, 5.82 mmol) in THF (84 mL) was added water (29 mL). After the solution was cooled to 0°C in an ice-bath for 15 min, 30% hydrogen peroxide (3.75 mL, 32.6 mmol) was added dropwise, followed by the dropwise addition of lithium hydroxide monohydrate (0.54 g, 12.8 mmol) in water (3.0 mL). The clear solution was stirred at 0°C for three hours. The reaction was monitored by TLC to secure completeness. The reaction was quenched by the dropwise addition of 1.3 M sodium sulfite (28 mL) in an ice bath, then the solution was allowed to warm up to room temperature and stirred for 30 mins. Volatiles were removed by rotary evaporation, and the residue aqueous phase was extracted with dichloromethane to remove the chiral auxiliary for recycle. The remaining aqueous phase was cooled to 0°C and acidified to pH=1 with 6 N HCl solution, and extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a light yellow oil, 0.94g(70%).

(2S,3S)-2-Azido-3-phenylisohexanoic acid (11): Pale yellow oil (75%), R_f=0.32(II), $[\alpha]^{20}_D$= -15.2° (c= 0.4, $CHCl_3$). ^{1}H NMR: δ ppm 10.6(s, 1H, broad, -COOH), 7.28-7.18(m, 5H, aromatic hydrogens),

4.51(d, J=7.0 Hz, -C_αH-), 2.79(t, J=7.3, 1H, -C_βH-), 2.15(m, 1H, -$CH(CH_3)_2$), 1.07(d, J=6.7Hz, -CH_3), 0.73(d, J=6.7Hz, -CH_3); ^{13}C NMR δ ppm 176.0, 137.7, 129.2, 128.9, 128.3, 128.1, 127.3, 63.9, 54.0, 29.3, 20.9, 20.4. IR (film, cm^{-1}): 3500~2500, 2957, 2115, 1712, 1599, 1386, 1367, 1265, 1074, 913, 703. MS for $C_{12}H_{15}O_2N_3$, Calcd: 233.1164 (M^+); Found 234.1255(M^++H).

(2R,3R)-2-Azido-3-phenylisohexanoic acid (12): Pale yellow oil (73%), R_f=0.34(**III**), $[\alpha]^{20}_D$=+12.5° (c= 0.5, $CHCl_3$). ^{1}H NMR: δ ppm 10.6(s, 1H, broad, -COOH), 7.28-7.18(m, 5H, aromatic hydrogens), 4.51(d, J=7.0 Hz, -C_αH-), 2.80(t, J=7.3, 1H, -C_βH-), 2.15(m, 1H, -$CH(CH_3)_2$), 1.08(d, J=6.7Hz, -CH_3), 0.73(d, J=6.7Hz, -CH_3); ^{13}C NMR δ ppm 176.0, 137.7, 129.2, 128.9, 128.3, 128.1, 127.3, 63.9, 54.0, 29.3, 20.9, 20.4. IR (film, cm^{-1}): 3500~2500, 2959, 2116, 1713, 1600, 1386, 1367, 1266, 1075, 913, 703. MS for $C_{12}H_{15}O_2N_3$, Calcd:. 233.1164 (M^+); Found 234.1251(M^++H).

(2R,3S)-2-Azido-3-phenylisohexanoic acid (13): Pale yellow oil (70%), R_f=0.30(**II**), $[\alpha]^{20}_D$= -27.5° (c=1.0, $CHCl_3$). ^{1}H NMR: δ ppm 9.14(s, broad, 1H, -COOH), 7.31-7.15(m, 5H, aromatic hydrogens), 4.18(d, J=7.0 Hz, -C_αH-), 2.94(t, J=7.3 Hz, 1H, -C_βH-), 2.30(m, 1H, -$CH(CH_3)_2$), 0.95(d, J=6.7Hz, -CH_3), 0.78(d, J=6.7Hz, -CH_3); ^{13}C NMR: δ ppm 175.6, 138.5, 129.4,128.9, 128.3, 128.0, 127.4, 64.6, 53.4, 28.7, 21.0, 19.4. IR (film, cm^{-1}): 3500~2500, 2957, 2115, 1712, 1599, 1386, 1367, 1265, 1074, 913, 703. MS for $C_{12}H_{15}O_2N_3$, Calcd.: 233.1164 (M^+); Found 234.1258(M^++H).

(2S,3R)-2-Azido-3-phenylisohexanoic acid (14): Pale yellow oil (72%), R_f= 0.31(**II**), $[\alpha]^{20}_D$= +17.5(c=1.2, $CHCl_3$). ^{1}H NMR: δ ppm 9.13(s, broad, 1H, -COOH), 7.31-7.15(m, 5H, aromatic hydrogens), 4.18(d, J=7.0 Hz, -C_αH-), 2.94(t, J=7.3 Hz, 1H, -C_βH-), 2.30(m, 1H, -$CH(CH_3)_2$), 0.95(d, J=6.7Hz, -CH_3), 0.78(d, J=6.7Hz, -CH_3); ^{13}C NMR δ ppm 175.4, 138.6, 129.3, 128.9, 128.0, 127.4, 64.7, 53.4, 28.7, 21.0, 19.4. IR (film, cm^{-1}): 3500~2500, 2959, 2116, 1713, 1600, 1386, 1367, 1266, 1075, 9134, 703. MS for $C_{12}H_{15}O_2N_3$, Calcd: 233.1164 (M^+); Found 234.1253(M^++H).

General Procedures for the Reduction of the Azido Acids. Illustrated by preparation of (2R,3R)-2-amino-3-phenylisohexanoic acid: A solution of azide acid **12** (0.94 g, 4.0 mmol) in 100% ethanol (22 mL) and 6 N HCl (1.0 mL) in a hydrogenation vessel was bubbled with Argon for 5 min to remove air, and then 10% Pd/C(0.2 g) was added. The reaction vessel was emptied and refilled with H_2 three times, and shaken under 28 psi H_2 for 3 hours. The catalyst was filtered out through celite, and washed with 100% ethanol (3 x 20 mL), and the volatiles were removed by rotary evaporation. The residue was loaded on a coolant jacked ion-exchange column filled with Amberlite IR-120(H^+) resin (40 g). The column was washed with deionized water until the eluent was neutral. The amino acid was washed off the column with 20% NH_4OH solution, the fractions containing the product were combined and evaporated to remove the NH_3, then frozen and lyophilized to give the title compound as an off-white solid.

(2S,3S)-2-Amino-3-phenylisohexanoic Acid (15). White solid (84%), decomposed at 160°C, R_f= 0.76 (**III**) on chiral TLC plate, $[\alpha]^{20}_D$= +21.0° (c=0.1, methanol). ^{1}H NMR(D_2O): δ ppm 7.26-7.05(m, 5H, -C_6H_5), 3.96(d, J=5.5Hz, 1H, -C_αH-), 2.81(dd, J=9.1, 5.5Hz, 1H,-C_βH-), 2.01(m, 1H, -$CH(CH_3)_2$], 0.84(d, J=6.6 Hz, 3H, -CH_3), 0.63(d, J=6.6 Hz, 3H, -CH_3); IR (KBr, cm^{-1}): 3500~2500, 3409, 2971, 1739, 1650, 1493, 1390, 1369, 1203, 1133, 707. MS for $C_{12}H_{17}O_2N$, Calcd. 207.1259; Found 208.1335 (M^++H).

(2R,3R)-2-Amino-3-phenylisohexanoic Acid (16). White solid (85%), decomposed at 160°C, R_f=0.49 (**III**) on chiral TLC plate. $[\alpha]^{20}_D$= -21.8° (c=0.1, methanol). ^{1}H NMR(D_2O): δ ppm 7.26-7.05(m, 5H, -C_6H_5), 3.96(d, J=5.5Hz, 1H, -C_αH-), 2.81(dd, J=9.1, 5.5Hz, 1H,-C_βH-), 2.01[m, 1H, -$CH(CH_3)_2$], 0.84(d, J=6.6 Hz, 3H, -CH_3), 0.63(d, J=6.6 Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3500~2500, 3420, 2973, 1742, 1650, 1390, 1369, 1204, 1134, 707. MS for $C_{12}H_{17}O_2N$, Calcd. 207.1259; Found 208.1338 (M^++H).

(2R,3S)-2-Amino-3-phenylisohexanoic Acid (17). White solid (85%), decomposed at 185°C, R_f=0.55 (**III**) on chiral TLC plate. $[\alpha]^{20}_D$= -5.7° (c=0.1, methanol). ^{1}H NMR(D_2O): δ ppm 7.25-7.08(m, 5H, -C_6H_5), 4.05(d, J=4.6Hz, 1H, -C_αH–), 2.52(dd, J=10.0, 5.4Hz, 1H, -C_βH–), 2.28(m, 1H, –$CH(CH_3)_2$], 1.02(d, J=6.4Hz, 3H, -CH_3), 0.54(d, J=6.4Hz, 3H, -CH_3); IR (KBr, cm^{-1}): 3500~2500, 3433, 2965, 1729, 1650, 1389, 1339, 1200, 1146, 704. MS for $C_{12}H_{17}O_2N$, Calcd. 207.1259; Found: 208.1332 (M^++H).

(2S,3R)-2-Amino-3-phenylisohexanoic Acid (18) White solid (82%), decomposed at 185°C, R_f= 0.74 (**III**) on chiral TLC plate. $[\alpha]^{20}_D$= +3.8° (c=0.1, methanol). ^{1}H NMR(D_2O): δ ppm 7.25-7.08(m, 5H, -C_6H_5), 4.05(d, J=4.6Hz, 1H, -C_αH–), 2.52(dd, J=10.0, 5.4Hz, 1H, -C_βH–), 2.28(m, 1H, –$CH(CH_3)_2$], 1.02(d, J=6.4Hz, 3H, -CH_3), 0.54(d, J=6.4Hz, 3H, -CH_3); IR (KBr, cm^{-1}): 3500~2500, 3421, 2963, 1739, 1651, 1389, 1339, 1195, 704. MS for $C_{12}H_{17}O_2N$, Calcd. 207.1259; Found 208.1335 (M^++H).

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