New Amino Acids for the Topographical Control of Peptide Conformation: Synthesis of All the Isomers of α,β-Dimethylphenylalanine and α,β-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid of High Optical Purity

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The synthesis of all four diastereoisomers of α,β-dimethylphenylalanine (4) as well as those of α,β-dimethyl-1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid (5 and 6) have been accomplished in high yield and high optical purity. Molecular mechanics calculations on the N^{α}-acetyl and *N*-methylcarboxamide derivatives of (3*R*,4*R*)-6 and (3*R*,4*S*)-5 indicate large and moderate energy stabilization for the gauche(−) but not the gauche(+) side-chain conformers of (3*R*,4*S*)-5 and (3*R*,4*R*)-6, respectively. By symmetry rules, the same holds for (3*S*,4*R*)-5 and (3*S*,4*S*)-6, respectively. Thus, these amino acids are potential building blocks for the topographical design of peptides (Kazmierski et al., *J. Am. Chem. Soc.* **1991**, *113*, 2275–2283) by providing acylated 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives in which a gauche(−) and not a gauche(+) side-chain conformation is energetically more stable for the L amino acid. Synthetic details and implications of these new amino acids for peptide and protein design are discussed.

Introduction

Designing specific three-dimensional structures of peptides and proteins is one of the most challenging problems of bioorganic chemistry[1] and is of great interest because of its possible applications in medicine[1,2] and chemistry.[3] From the structural point of view, a rational approach requires constraining the dihedral angles characterizing a particular peptide conformation (e.g. Φ, ψ, ω, and χ_1) (Figure 1) to values required by a desired three-dimensional structure (e.g. α-helix Φ = ±55°, ψ = ±60°). For this purpose, several approaches for the design of specific secondary structures, or for structures that will induce them to form, have been proposed.[4] However, very little attention has been paid to constraining the χ_1 angle such that the local topography of the peptide can be controlled. Recently, we have found theoretically and experimentally[5-7] that 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) prefers a gauche(−) side-chain conformation (χ_1 = −60° for an L and +60° for a D configuration) in a free *N*-amino form, while N-acylation leads to a gauche(+) side-chain conformation (χ_1 = +60° for L, and −60° for D configurations) of Tic (Figure 2). These findings have had a profound influence on the way we have designed a series of short cyclic octapeptides derived from the somatostatin

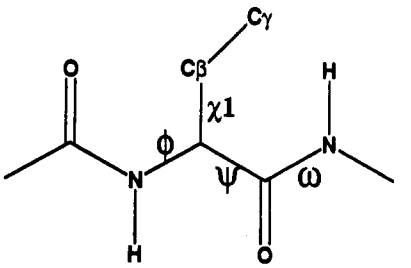

Figure 1. Standard IUPAC nomenclature of amino acid dihedral angles : Φ (C′–N–C_α–C′); ψ (N–C_α–C′–N); ω (C_α–C′–N–C_α); χ_1 and (N–C_α–C_β–C_γ).

R, g(+) R, g(-)

Figure 2. Gauche(−) (χ_1 = −60°) and gauche(+) (χ_1 = 60°) side-chain conformers of D-1,2,3,4-tetrahydrioisoquinoline-3-carboxylic acid.

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(4) For recent reviews see: ref 1a and Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287–300. For additional references see: (a) Feigel, M. *J. Am. Chem. Soc.* **1986**, *108*, 181–182. (b) Kemp, D. S.; Carter, J. S. *Tetrahedron Lett.* **1987**, *28*, 4645–4648. (c) Sato, K.; Nagai, V. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1231–1242. (d) Kemp, D. S.; Bowen, B. R. *Tetrahedron Lett.* **1988**, *29*, 5081–5082. (e) Kemp, D. S.; Curran, T. P. *Tetrahedron Lett.* **1988**, *29*, 4935–4938. (f) Kemp, D. S.; Carter, J. S. *J. Org. Chem.*, **1989**, *54*, 109–115. (g) Zabrocki, Z.; Smith, G. D.; Dunbar, J. B., Jr.; Iiyama, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875–5880.

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(6) (a) Kazmierski, W. M.; Hruby, V. J. *Tetrahedron* **1988**, *44*, 697–710. (b) Kazmierski, W. M.; Wire, W. S.; Lui, G. K.; Knapp, R. J.; Shook, J. E.; Burks, T.F.; Yamamura, H. I.; Hruby, V. J. *J. Med. Chem.* **1988**, *31*, 2170–2177.

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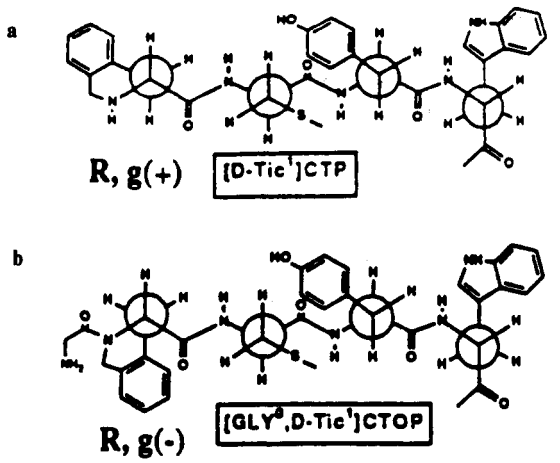


Figure 3. Newman representations of the core amino acid side-chain conformations for D-Tic and Tyr emphasize their topographical arrangement for high (a) and low (b) potency and selectivity at the μ-opioid receptor.[5-7] (a) D-Tic-Cys-Tyr-D-Trp-Lys-Thr-Pen-The-NH_2. (b) Gly-D-Tic-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2.

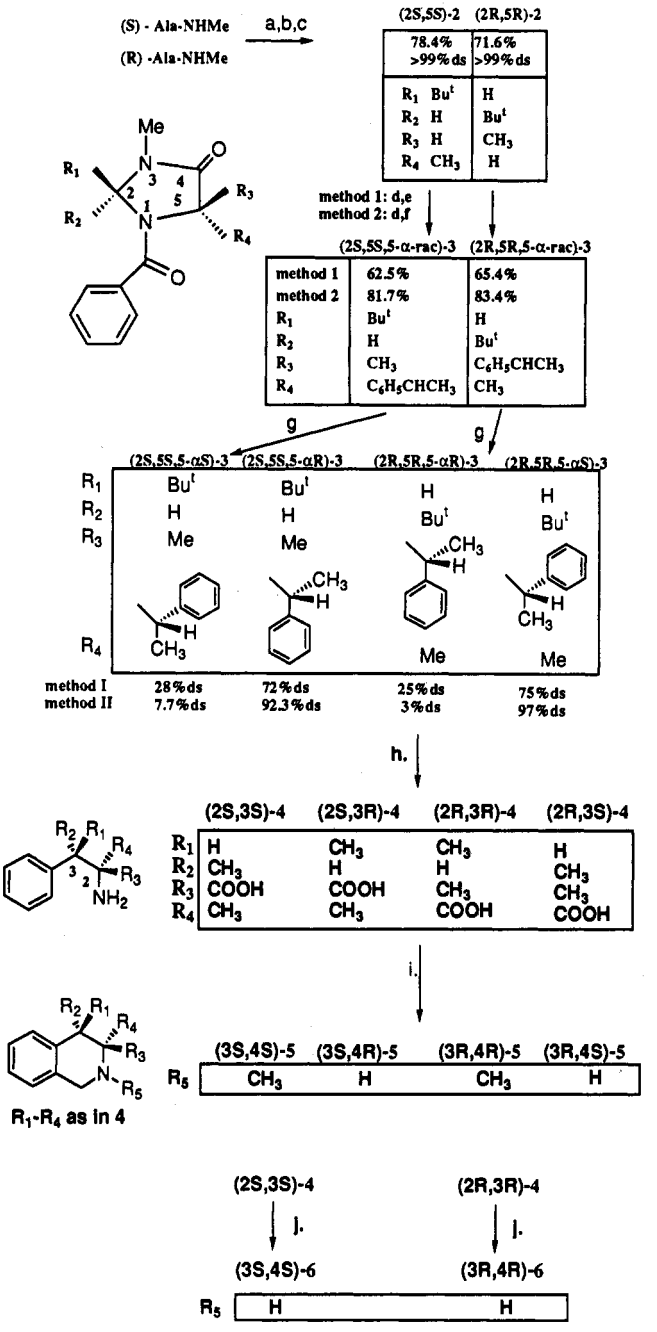
and possessing high affinity and selectivity for μ opioid receptors.[6] Briefly, we could correlate high μ opioid receptor potency of the peptide D-Tic-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH_2 (**10**) with a gauche(+) side-chain conformation of D-Tic[1], enabling it to be located on the same side of the molecule as another important pharmacophore, the Tyr[3] aromatic side chain (Figure 3a). Coupling of Gly to **10** resulted in a peptide, Gly-D-Tic-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH_2, **11**, in which the D-Tic residue had a gauche(-) side-chain conformation positioning this pharmacophore on the opposite side of the molecule relative to the Tyr[3] pharmacophore (Figure 3b) with a corresponding significant loss of potency. These and other examples of the successful uses of the Tic residue in bioactive peptide design prompted us to consider the design and synthesis of Tic analogues with complementary conformational properties, that is a gauche(-) side-chain conformation for the N-acylated L-Tic derivative and a gauche(+) for a N-terminal free L-amino acid, to broaden the arsenal of amino acids and their mimetics available in peptide and protein design. In this contribution, we report the design rationale and the synthesis of all four stereoisomers of α,β-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid—potential new building blocks for topographical design of peptides.

Results

Synthesis of the Four Stereoisomers of α,β-Dimethylphenylalanine. In our retrosynthetic scheme, we were looking for the simplest process capable of establishing both the α and β chiral centers in a single step. We reasoned that modification of some existing methodology of amino acid synthesis[8] might be capable of doing this chemistry, though we found no literature precedent for such a highly sterically hindered process.[9] Eventually, we found that adaptation of chemistry developed by Seebach and co-workers[9,10] could be used for this purpose.

Both the *S* and *R* enantiomeric forms of alanine *N*-methylamide were condensed with pivalaldehyde in the presence of diisopropylethylamine (DIEA) and anhydrous $MgSO_4$, to yield the two enantiomeric imines (not shown in the Scheme 1). We have found these reaction conditions superior to those originally described.[10] In the next step,

Scheme 1



[a] (a) Bu^tCHO, $MgSO_4$, DIEA, DCM, 0 °C to rt, 24 h; (b) CH_3COCl, EtOH, 0 °C to rt, 5 h; (c) C_6H_5COCl, DIEA, DCM, 0 °C to rt; (d) LDA, -78 °C, THF; (e) $C_6H_5CH(Br)CH_3$ (racemic, equimolar); (f) $C_6H_5CH(Br)CH_3$ (racemic, 3-fold excess); (g) crystallization; (h) 6 N HCl, 150 °C, sealed ampule; (i) 37% aqueous HCHO, HCl (concd), reflux; (j) paraformaldehyde, 6 N HCl, 170 °C, 15 h, sealed ampule.

(8) For recent developments in the asymmetric synthesis of amino acids see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: New York, 1989.

(9) For a comprehensive account of the reactivity of various electrophiles and nucleophiles see Fitzi, R.; Seebach, R. *Tetrahedron* **1988**, *44*, 5277–5298.

(10) Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135–143.

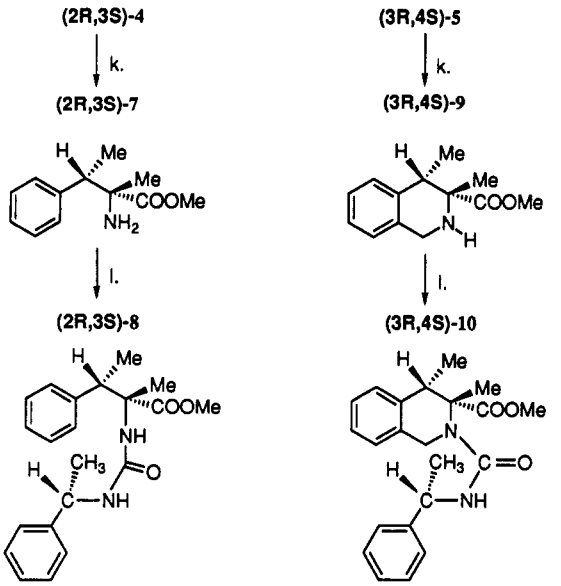
the imines were cyclized to (2*S*,5*S*)- and (2*R*,5*R*)-2-*tert*-butyl-3,5-dimethylimidazolidin-4-one, respectively. We observed higher yields and ease of reaction compared to previous procedures by preparing HCl in situ from ethanol and acetyl chloride. Under the reaction conditions, the product precipitated out as its HCl salt in high yield and in very high optical purity (only one diastereomer, ≥99% stereoselectivity as evaluated by NMR) in both cases. Consequent N-benzoylation of position 1 resulted in both the (2*S*,5*S*)- and (2*R*,5*R*)-1-benzoyl-2-*tert*-butyl-3,5-dimethylimidazolidin-4-ones, (2*S*,5*S*)-**2** and (2*R*,5*R*)-**2**, respectively, in high yield (Scheme 1).

In the next step, racemic (1-bromoethyl)benzene was reacted with the anion (generated by LDA) of (2*S*,5*S*)-**2** and (2*R*,5*R*)-**2** under two sets of conditions. In the first experiment, an equivalent amount of (1-bromoethyl)-benzene was used. We anticipated that under these alkylation conditions both enantiomers of (1-bromoethyl)-benzene would be incorporated in significant yields, resulting in (2*S*,5*S*,5-α-rac)-**3** and (2*R*,5*R*,5-α-rac)-**3**. Indeed, we observed 28% of (2*S*,5*S*,5-α*S*)-**3** and 72% of (2*S*,5*S*,5-α*R*)-**3**, and 25% of (2*R*,5*R*,5-α-*R*)-**3** and 75% of (2*R*,5*R*,5-α*S*)-**3** (Scheme 1). We were able to separate the diastereoisomers by recrystallization from ethyl acetate or ethyl acetate/petroleum ether mixtures (see Experimental Section).

In the second experiment, reaction conditions were designed to obtain (2*S*,5*S*,5-α*R*)-**3** and (2*R*,5*R*,5-α*S*)-**3** in high optical purity by using a large (3-fold) excess of (1-bromoethyl)benzene. Indeed, under these kinetic resolution conditions, both compounds were synthesized with high overall yields (over 80%) and high optical purities, virtually without further need for diastereomeric enrichment by crystallization (Scheme 1). Thus, the methods of Scheme 1 afforded a large-scale synthesis (we have used as much as 50 g in one step) of diastereosomers (2*S*,5*S*,5-α*R*)-**3** and (2*R*,5*R*,5-α*S*)-**3**. A moderate-scale (grams) separation of diastereomers (2*S*,5*S*,5-α*S*)-**3** and (2*R*,5*R*,5-α*R*)-**3** also has been accomplished. The stereochemistry of the asymmetric centers were determined as described below (*vida infra*). All of the four optically pure **3** were then hydrolyzed and the products purified by ion-exchange chromatography to give the corresponding four diastereomers of α,β-dimethylphenylalanine (2*S*,3*S*)-**4**, (2*S*,3*R*)-**4**, (2*R*,3*R*)-**4**, and (2*R*,3*S*)-**4**.

Synthesis of All Four Stereoisomers of α,β-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid. We next examined the conversion of **4** into their respective tetrahydroisoquinoline derivatives using Pictet–Spengler conditions.[11] High yields were obtained in the case of (2*S*,3*R*)-**4** → (3*S*,4*R*)-**5** and (2*R*,3*S*)-**4** → (3*R*,4*S*)-**5** (Scheme 1), while in the remaining cases *N*-methyl products of tetrahydroisoquinoline were isolated. We reasoned that in these cases, the imine RNH=CH_2 was formed first from condensation of formaldehyde and the amino acid. In the next step, two competing reactions could occur, one involving nitrogen protonation and subsequent ring closure (S_E) to the tetrahydroisoquinoline, and the other involving reduction of the imine under Pictet–Spengler conditions by the residual formic acid to the *N*-methylamine, followed by condensation with another molecule of formaldehyde and cyclization to the *N*-methyltetrahydroisoquinoline (Scheme 1). Apparently, the overall topography and lack of steric constraints during the cyclization to (3*S*,4*R*)-**5** and (3*R*,4*S*)-**5** (mirror images) allows the first reaction to take place readily, before the competing reaction can take place.

Scheme 2



[a] (k) $SOCl_2$, MeOH, reflux, 4 h; (l) (−)-(*S*)-α-methylbenzyl isocyanate, DMAP.

In the other case, however, both (2*S*,3*S*)-**4** and (2*R*,3*R*)-**4** experience unfavorable α,β-methyl steric repulsions during formation of the six-membered ring, making cyclization slow relative to the competing reduction. Thus, the imine is reduced first and only then cyclized to the *N*-methyltetrahydroisoquinoline. To overcome this side reaction, we have modified the Pictet–Spengler reaction conditions by using paraformaldehyde, exhaustive deoxygenation of the reaction medium, and carrying out the reaction in a sealed tube at >170 °C for 12 h. A high-yield synthesis of both (3*S*,4*S*)-3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [(3*S*,4*S*)-**6**] and (3*R*,4*R*)-3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [(3*R*,4*R*)-**6**] (Scheme 1) (see Experimental Section for details) was obtained.

Proof of the Optical Purity of (2*R*,3*S*)-4 and (3*R*,4*S*)-5. We have converted both (2*R*,3*S*)-**4** and (3*R*,4*S*)-**5** to their methyl ester *N*,*N*′-urea derivatives (2*R*,3*S*)-**8** and (3*R*,4*S*)-**10**, by reacting their methyl ester derivatives (2*R*,3*S*)-**7** and (3*R*,4*S*)-**9**, respectively (Scheme 2), with (−)-(*S*)-α-methylbenzyl isocyanate[12a] in the presence of (dimethylamino)pyridine (DMAP). In each case, only a single set of ^1H NMR signals was observed confirming the optical purity of (2*R*,3*S*)-**4** and (3*R*,4*S*)-**5**, as well as the other amino acids related to them through NMR or optical rotation comparisons (see Experimental Section). The limits of detection of the diastereoisomer are about 1%

Determination of the Absolute Configuration of (2*S*,5*S*,5-α*S*)-3. We have determined the X-ray structure of (2*S*,5*S*,5-α*S*)-**3** (Figure 4).[12b] By symmetry, (2*S*,5*S*,5-α*R*)-**3** must be represented by a 2*S*,5*S*,5-α*R* configuration. The stereochemistry of the remaining compounds (2*R*,5*R*,-

(11) Pictet, A.; Spengler T. *Chem. Ber.* 1911, *44*, 2030–2036.

(12) (a) Rice, K.; Brossi, A. *J. Org. Chem.* 1980, *45*, 592–601. (b) The author has deposited atomic coordinates for this structure (accession no. SOSDEJ) with the Cambridge Crystallographic Data. Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

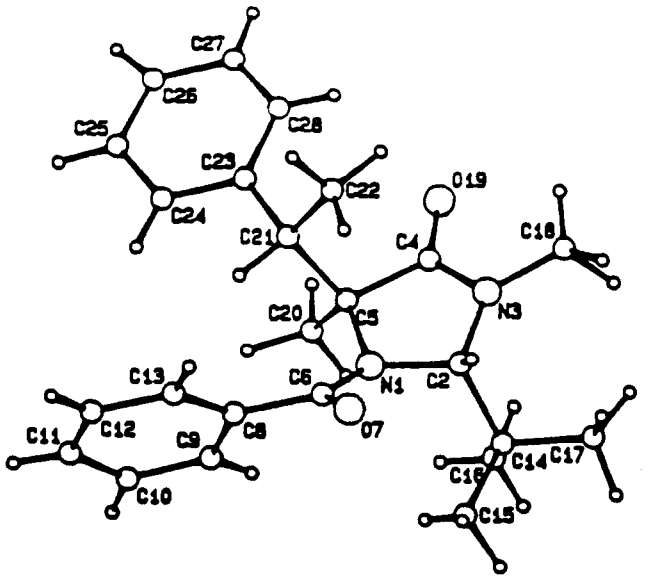


Figure 4. The X-ray structure for (2*S*,5*S*)-1-benzoyl-2-*tert*-butyl-3-methyl-5-(α(*S*)-methylbenzyl)imidazolidin-4-one [(2*S*,5*S*,5-α*S*)-**3**].

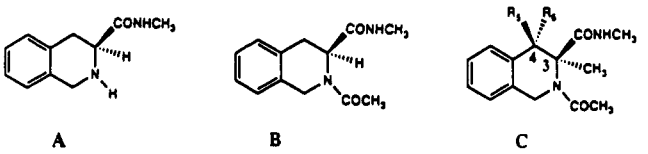


Figure 5. Structures of D-1,2,3,4-tetrahydroisoquinoline-3-*N*-methylcarboxamide (**A**), *N*-acetyl-D-1,2,3,4-tetrahydroisoquinoline-3-N-methylcarboxamide (B), and *N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-*N*-methylcarboxamide (C). The stereochemistry of position 4 in *C* can be found in Scheme 2.

5-α*R*)-**3** and (2*R*,5*R*,5-α*S*)-**3** was deduced by comparing the NMR and optical rotation data for all four isomers of **3**.

Discussion and Computational Results

The results discussed thus far make it clear that the configuration in position 2, as well as position 3 (β) of the phenylalanine backbone is of great importance for the ease of cyclization of substituted phenylalanines to their respective tetrahydroisoquinolines. Thus, we had reasonable expectations that a desired conformation of the pipecolic acid moiety could be controlled by proper choice of the β-configuration.

To better understand the possible conformational preferences, we have performed exhaustive energy minimization calculations of angle grid search-generated conformers of 1,2,3,4-tetrahydroisoquinoline-3-*N*-methylcarboxamide (Tic-NHMe), of N^{α}-acetyl-1,2,3,4-tetrahydroisoquinoline-*N*-methylcarboxamide (Ac-Tic-NHMe), and of *N*-acetyl-3,4-dimethyltetrahydroisoquinoline-3-*N*-methylcarboxamide (Ac-(3,4-Me_2)Tic-NHMe) (Figure 5). Bonds N^2–C(O) and C^3(O)–N in all these molecules were rotated by 30° increments and all geometrically reasonable starting conformations of the pipecolic acid ring were considered. Considering both possible side-chain conformers of Tic-NHMe, the gauche(−) conformer, as expected, was found to be more stable than the gauche(+) (Table 1) conformer (Figure 2). This geometrical preference is inverted in Ac-Tic-NHMe, with the gauche(+) conformer being somewhat more stable, in agreement with

Table 1. Energies Generated from a Grid Search and Energy Minimization Calculation for 1,2,3,4-Tetrahydroisoquinoline-3-*N*-methylcarboxamide (A), *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline-3-*N*-methylamide (B), and *N*-Acetyl-3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-*N*-methylamide (C). (All three amino acid derivatives are of the D configuration. Structures are shown in Figure 5).

		side-chain conformation			
		D, gauche(−)		D, gauche(+)	
		energy (Kcal/mol)	χ_1 angle (deg)	energy (kcal/mol)	χ_1 angle (deg)
A	4*S*,3*R*	13.674	−72.1	11.939	62.0
B	4*S*,3*R*	7.750	−65.8	7.901	53.7
C	4*S*,3*R*	22.329	−71.2	8.844	55.4
	4*R*,3*R*	16.696	−63.9	11.654	51.6

previous experimental results.[5,6,13] By symmetry rules, the stable conformations for D-Tic-NHMe and Ac-D-TicNHMe are D gauche(+) and D gauche(−), respectively.

Interestingly, 4*S*,3*R* "dimethylation" of Ac-Tic-NHMe, leading to Ac-(3*R*,4*S*-Me_2)Tic-NHMe caused another inversion of the side-chain conformational preference to the D gauche(+) conformation, preferred over the D gauche(−) conformation by 14.5 kcal/mol (Table 1). The same trends, though of a smaller magnitude, are found for the diastereoisomeric Ac-(3*R*,4*R*-Me_2)Tic-NHMe. Here, the energy difference between the side-chain rotamers is only ca. 5 kcal/mol, but still indicates a fairly large stabilizing effect of both α and β methyl groups for a D gauche(+) conformation (Table 1). These results indicate that 3,4-dimethylation is capable of changing the χ_1 conformational preference of Ac-D-Tic-NH-Me to D gauche-(+), the effect being stronger for the 3*R*,4*S* than for the 3*R*,4*R* isomers. Based on symmetry considerations, the same is valid for 3*S*,4*R*, and 3*S*,4*S*, respectively. Figure 6 presents the lowest energy conformers for D gauche(−) [3*R*,4*S*]; D gauche(+) [3*R*,4*S*], D gauche(−) [3*R*,4*R*]; and D gauche(+) [3*R*,4*R*], oriented with their C_β–C_α axis perpendicular to the plane of the drawing. It is clear that a gauche (ca. 30°) relationship of both the α- and β-methyl groups in D gauche(−) [3*R*,4*S*] makes this conformation much less stable than in D gauche(+) [3*R*,4*S*], where they are in a *trans* relationship. On the other hand, the dihedral angle C_{Me}–C_β–C_α–C_{Me} (ca. 60° for both D gauche(−) [3*R*,-4R] and D gauche(+) [3*R*,4*R*] makes the energy distinction between them less pronounced than for the former pair.

We believe that the slow Pictet–Spengler cyclization rates for (2*S*,3*S*)-**4** and (2*R*,3*R*)-**4** compared to (2*S*,3*R*)-**4** and (2*R*,3*S*)-**4** can be rationalized in terms of the low-energy conformers in Figure 6. Providing that the D gauche(+) conformation is of the lowest energy for 3*R*,4*R* (Table 1), it is clear that in (2*R*,3*R*)-**4**, D gauche(+) [3*R*,4*R*], the gauche arrangement of both the α-Me and β-Me groups requires that a considerable energy barrier be overcome in order to complete the cyclization (Figure 6). By symmetry rules, the same will hold for (2*S*,3*S*)-**4**. In contrast for (2*R*,3*S*)-**4**, an anti configuration of both the α-Me and β-Me in D gauche(+) [3*R*,4*S*] makes the cyclization a fast process, and by symmetry rules, the same will hold for (2*S*,3*R*)-**4**; the cyclization is fast and devoid of competing side reactions.

(13) Kazmierski, W. M.; Yamamura, H. I.; Burks, T. F.; Hruby, V. J. In *Peptides 1988, Proceedings of the 20th European Peptide Symposium*; Jung, G., Bayer, E., Eds.; Walter de Gruyter: New York, 1989; pp 643–645.

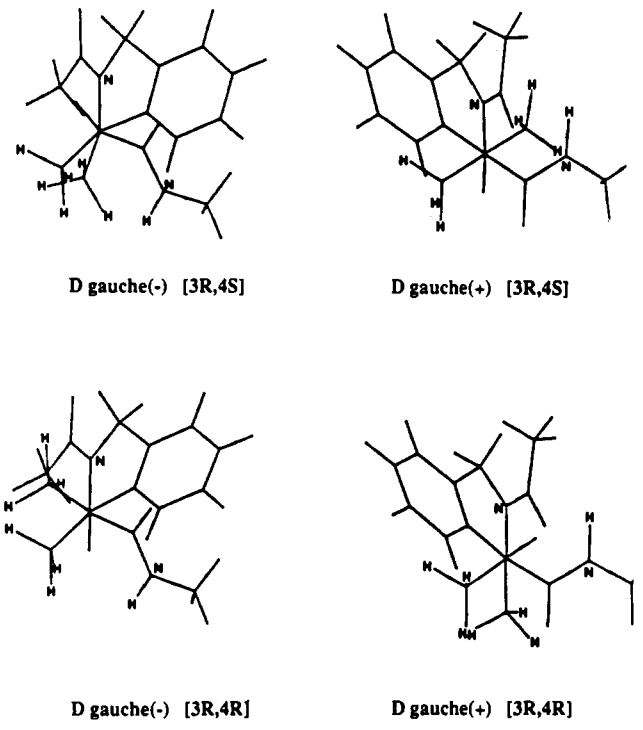


Figure 6. Lowest energy D gauche(−) conformers (left column) and D gauche(+) conformers (right column) of 3*R*,4*S* (upper row) and 3*R*,4*R* (bottom row) diastereomers of *N*-Ac-3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-*N*-methylcarboxamide (**C**). All hydrogen representation. Note steric interaction of both 3- and 4-methyl groups in D g(−) [3*R*,4*S*] (high-energy conformer) and lack of it in D g(+) [3*R*,4*S*] (low-energy conformer). Steric differences for D g(−) [3*R*,4*R*] and D g(+) [3*R*,4*R*] are less pronounced, with D g(+) [3*R*,4*R*] energetically favored.

In summary, we have successfully synthesized all four diastereoisomers of α,β-dimethylphenylalanine **4**, as well as of 3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **5**. On the basis of energetic considerations supported by the results of Pictet–Spengler cyclization, we have proposed that **5** should have stable D gauche(+) or L gauche(−) side-chain conformations. Thus, we are able to expand the repertoire of building blocks for the design of topographically controlled templates.[5] In addition, using similar energetic arguments, we can rationalize the distinct rates of cyclizations of (2*S*,3*S*)-**4** and (2*R*,3*R*)-**4** on one hand, and (2*S*,3*R*)-**4** and (2*R*,3*S*)-**4** on the other, to tetrahydroisoquinolines. Currently we are in the process of incorporating them into peptides. Their NMR and X-ray derived conformations will be presented in due course.

Experimental Section

^{1}H NMR spectra were recorded on 250-MHz NMR spectrometers at 250 MHz and on a 500-MHz NMR spectrometer at 500 MHz. All of the ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer. The solvent used was $CDCl_3$ (Aldrich, 99.8 atom % D) or D_2O (Aldrich, 100.0 atom % D) with dioxane as an internal reference. Mass spectra were recorded on a Hewlett-Packard 5988 A (University of Arizona Microanalysis Center) using either CI or EI techniques. Elemental analyses were performed by Desert Analytics (Tucson, AZ). Optical rotations were measured on an Autopol III (Rudolph Research, Fairfield, NJ). Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. For preparative chromatography silica gel (70–230 mesh, 60 Å, Aldrich) was used. Analytical thin-layer chromatography (TLC) was performed on polyester-backed 0.25-mm silica gel $60F_{254}$ plates (Sigma, St. Louis). The solvent systems used were the following: A, 100% EtOAc; B, EtOAc/pentane, 1/2 (v/v); C, EtOAc/pentane, 1/7 (v/v). THF was freshly distilled from sodium/benzophenone. Diisopropylethylamine (99% pure, Aldrich) was distilled from CaH_2 and stored over 3-Å molecular sieves. (1-Bromoethyl)-benzene (Aldrich) was used as received or after passing through Al_2O_3 (activated, neutral, Brockmann I, 58 Å). All of the metalation and moisture-sensitive reactions and reagent transfers were carried out under Ar, and the glassware was oven dried for several hours, assembled hot, and cooled under Ar atmosphere.

Molecular Modeling Calculations. We have performed exhaustive energy minimizations on different starting conformers of Tic derivatives (Figure 5) using the Molecular Modeling Software SYBYL (version 5.3, November 1989, Tripos Associates, Inc., St. Louis, MO, mounted on a Silicon Graphics Personal IRIS). We generated a large number of starting conformations by incremental (30°) rotation of the N–C(O) and C(O)–NHMe dihedral angles starting with 20 pipecolic acid ring conformations including (both positive and negative) half-chair and half-boat conformations. The potential field utilized consisted of terms representing covalent bond stretching, bond angle bending, (improper dihedral for out-of-plane and out-of-tetrahedral configurations), dihedral torsions, and Coulombic and van der Waals interactions using standard SYBYL parameters and computational methods.

Preparation of (2*S*,5*S*)-1-Benzoyl-2-*tert*-butyl-3,5-dimethylimidazolidin-4-one [(2*S*,5*S*)-2]. HCl·L-Ala-NHMe (10 g, 0.0722 M) was suspended in 180 mL of DCM (in a 1-L round-bottom flask containing 20 g of $MgSO_4$), and 10.5 mL (0.0964 M) of pivalaldehyde was added, followed by 18.2 mL (0.1044 M) of freshly distilled diisopropylethylamine (DIEA) while cooling the reaction to 0 °C and vigorously stirring the suspension. The ice bath was allowed to melt on its own while continuing the reaction for 24 h. Filtration and rotary evaporation yielded pure imine (92.1% yield) that was cyclized in a solution of 100 mL of absolute EtOH by dropwise addition of 8.82 g (0.112 M) of CH_3COCl at −10 °C. Gradual warming to rt over 1 h resulted in precipitation of pure diastereomer (2*S*,5*S*)-2-*tert*-butyl-3,5-dimethylimidazolidin-4-one. *N*-Benzoylation was accomplished as reported,[10] yield 78.4% (for analytical data, see ref 10).

Mixture of (2*S*,5*S*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*R*)-methylbenzyl)-imidazolidin-4-one ((2*S*,5*S*,5-α*R*)-3) and (2*S*,5*S*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*S*)-methylbenzyl)imidazolidin-4-one ((2*S*,5*S*,5-α*S*)-3). Diisopropylamine (35.84 g (0.256 M) was placed in a 1-L round-bottom flask with 350 mL of THF and cooled to −78 °C, followed by the addition of 160 mL (0.256 M) of *n*-BuLi (1.6 M in hexane). In a separate flask, 58.4 g (0.213 M) of **2a** and 1350 mL of THF were combined and cooled to −78 °C, and the contents of the first flask gradually added via a cannula and left for 45 min until the solution turned red. This was followed by the addition of 38.75 g (0.213 M) of (1-bromoethyl)benzene (at −78 °C). The reaction was allowed to proceed until a yellow color persisted (ca. 60 h) while the ice bath melted on its own. The reaction mixture was then poured into 300 mL of saturated aqueous NH_4Cl and the mixture extracted with 500 mL of Et_2O (2×). The organic phases were combined, dried over $MgSO_4$, filtered and evaporated, resulting in a crude mixture which was purified on a silica gel column with 2:1 (v/v) petroleum ether/EtOAc mixture, yielding 50.4 g (62.5%) of a mixture of (2*S*,5*S*,5-α*S*)-**3** and (2*S*,5*S*,5-α*R*)-**3**, (28 and 72% or 1:2.5, respectively, by NMR). The diastereoisomers were separated by crystallization from 1/2 (v/v) EtOAc/petroleum ether. (2*S*,5*S*,5-α*R*)-**3** crystallizes first as large cubes, (2*S*,5*S*,5-α*R*)-**3** as needles. ^{1}H NMR of (2*S*,5*S*,5-α*S*)-**3** ($CDCl_3$) δ 7.7–6.7 (m, 10H), 5.76 (s, 1H), 3.09 (s, 3H), 3.00 (q, 1H, J = 7.15), 1.26 (s, 3H), 1.09 (d, J = 7.17, 3H), 1.06 (s, 9H); $[\alpha]^{25}_D$ = −106.9° (c = 0.569, $CHCl_3$); one peak on GC/MS $(M + 1)_{calcd}$ = 379, $(M + 1)_{found}$ = 379; TLC R_f = 0.66 (A), 0.43 (B), 0.08 (C); mp 130–132 °C.

NMR of (2*S*,5*S*,5-α*R*)-**3** ($CDCl_3$): major* and minor isomers were observed δ 7.80–6.60 (m, 10H), 4.86 (s, 0.38H), *4.80 (s, 0.62H), *4.25 (g, J = 7.37 Hz, 0.62H), 2.97 (q, J = 7.12 Hz, 0.38H), *2.90 (s, 1.77H), 2.53, (s, 1.23H), *2.00 (s, 1.77H), 1.65 (s, 1.23H), *1.55 (d, J = 7.40 Hz, 1.77H), 1.23 (d, J = 7.14 Hz, 1.23H), *0.91 (s, 5.58H), 0.65 (s, 3.42H); optical rotation $[\alpha]^{25}_D$ = 41.4° (c =

0.510, $CHCl_3$), one peak on GC/MS, $(M + 1)_{calcd}$ = 379 $(M + 1)_{found}$ = 379; TLC R_f = 0.66 (A), 0.43 (B), 0.08 (C); mp 129–132 °C.

(2*S*,5*S*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*R*)-methylbenzyl)imidazolidin-4-one (2*S*,5*S*,5-α*R*)-3. This reaction was carried out in a similar manner as above, except that a 3-fold excess of (1-bromoethyl)benzene was used resulting in the title compound in a reaction time (decolorization) of 12 h; recrystallized from 1/2 (v/v) EtOAc/petroleum ether; yield 81.7%.

(2*S*,3*R*)-2,3-Dimethylphenylalanine ((2*S*,3*R*)-4). (2*S*,5*S*,5-α*R*)-3 (0.40 g, 1.06 mM) was suspended in 10 mL of 6 N aqueous HCl in a glass hydrolysis tube, capped, and heated at 220 °C for 5 h or until all the residue reacted. The cooled contents were extracted with Et_2O (3×), and the water phase was evaporated off, yielding the hydrochloride salt of the title compound. Ion-exchange chromatography (Dowex 50×8–100, strongly acidic) with 1.3 N aqueous ammonia as an eluent and subsequent water hydrolysis of the ammonium salt resulted in the title compound (yield 75%; 0.19 g): ^1H NMR (D_2O) δ 7.08 (5H, m), 2.94 (q, 1H, 7.3 Hz), 1.03 (d, 3H, 7.3 Hz), 0.96 (s, 3H); ^{13}C NMR (D_2O) δ 179.95, 140.66, 129.04, 128.32, 127.32, 62.92, 45.77, 23.36, 14.96. MS (CI w/isobutane) $(M + 1_{calcd}$ = 194, $(M + 1)_{found}$ = 194. Anal. Calcd C, 68.37, H, 7.82, N 7.25. Found: C, 68.35; H, 7.65; 7.40; $[\alpha]^{25}_D$ = +20.7° (*c* = 0.458, MeOH).

(2*S*,3*S*)-2,3-Dimethylphenylalanine ((2*S*,3*S*)-4). The title compound was synthesized in a manner similar to (2*S*,3*R*)-4 in a yield of 82%: ^1H NMR (D_2O) δ 7.09 (m, 5H), 3.07 (q, 1H, 7.4 Hz), 1.14 (s, 3H), 1.11 (d, 7.4 Hz, 3H); ^{13}C NMR (D_2O) δ 178.60, 140.27, 128.52, 128.50, 127.43, 63.94, 44.78, 19.99, 13.77; MS (CI with isobutane), $(M + 1)_{calcd}$ = 194, $(M + 1)_{found}$ = 194; $[\alpha]^{25}_D$ = −31.7° (*c* = 0.492, MeOH). Anal. C, 68.37; H, 7.82; N, 7.25. Found: 68.34; H, 7.95; N, 7.19.

(3*S*,4*R*)-3,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*S*,4*R*)-5). A solution of (2*S*,3*R*)-4 (5.2 g, 26.94 mM) in 60.0 mL of HCl (37% aqueous) and 20.0 mL of HCHO (37% aqueous) was refluxed for 1 h and then continued for another 1.5 h after addition of 20.0 mL each of HCl (37% aqueous) and HCHO (37% aqueous). After evaporation, the product was converted to the title compound by ion-exchange chromatography (Dowex 50×8-100, strongly acidic) with 1.3 N aqueous NH_3, the eluent solvent. The solvent was evaporated and the ammonium salt hydrolyzed to yield 3.9 g (70.6%) of (3*S*,4*R*)-5: ^1H NMR (D_2O) δ 7.04 (m, 4H), 4.19 (d, 1H, 16.7 Hz), 4.07 (d, 1H, 16.7 Hz), 2.93 (q, 1H, 7.3 Hz), 1.18 (s, 3H), 0.95 (d, 3H, 7.3 Hz); ^{13}C NMR (D_2O) δ 175.69, 136.31, 129.82, 128.17, 127.08, 125.81, 125.17, 63.89, 40.77, 38.39, 19.33, 18.72; MS (CI with isobutane) $(M + 1)_{calcd}$ = 206, $(M + 1)_{found}$ = 206; $[\alpha]^{25}_D$ = −91.4° (*c* = 0.466, MeOH). Anal. Calcd C, 70.22; H, 7.37; N, 6.82. Found: C, 70.32; H, 7.05; N, 7.03.

***N*-Methyl-3(*S*),(4*S*)-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*S*,4*S*)-5).** The title compound was synthesized as described for (3*S*,4*R*)-5: yield, 78.5%; ^1H NMR (D_2O) δ 7.11 (4H, m), 4.32 (1H, d, 16.4 Hz), 4.08 (1H, d, 16.4 Hz), 3.29 (q, 1H, 6.3 Hz), 1.11 (d, 3H, 6.9 Hz), 0.99 (s, 3H); ^{13}C NMR (D_2O) δ 174.70, 134.60, 130.92, 126.99, 126.55, 126.40, 72.02, 51.78, 38.87, 38.62, 13.04, 7.54; MS (CI with isobutane) $(M + 1)_{calcd}$ = 220, $(M + 1)_{found}$ = 220, other peaks found: (M − COOH) = 174, $(M - CH_3)$ = 204; $[\alpha]^{25}_D$ = −54.5° (*c* = 0.433, MeOH).

(3*S*,4*S*)-3,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*S*,4*S*)-6). A 0.10-g sample of (2*S*),3*S*)-4 was combined with 0.50 g of paraformaldehyde $(CH_2O)_n$ and 6 mL of 6 N aqueous HCl in a thin-wall Pyrex tube. The slurry was carefully degassed, capped, and heated at 170 °C for 10 h. Evaporation and conversion of the hydrochloride salt to a free amino acid (as for (3*S*,4*R*)-5) resulted in 0.076 g (0.37 mM, 72.0% yield) of title compound: ^1H NMR (D_2O) δ 7.18–7.00 (m, 4H), 4.18 (d, 1H, *J* = 16.0 Hz), 4.00 (d, 1H, *J* = 16.0 Hz), 3.17 (q, 1H, *J* = 7.4 Hz), 1.21 (s, 3H), 1.06 (d, 3H, *J* = 7.4 Hz); ^{13}C NMR (D_2O) δ 178.7, 138.3, 128.4, 128.2, 127.4, 126.8, 126.2, 63.6, 42.5, 37.6, 19.7, 16.0; MS (CI with isobutane) $(M + 1)_{calcd}$ = 206, $(M + 1)_{found}$ = 206; $[\alpha]^{25}_D$ = −16.7° (*c* = 0.45; MeOH). Anal. Calcd C, 70.22, H, 7.37, N, 6.82. Found: C, 70.33, H, 7.32, N, 6.47.

(2*R*,5*R*)-1-Benzoyl-2-*tert*-butyl-3,5-dimethylimidazolidin-4-one ((2*R*,5*R*)-2) was obtained similarly to (2*S*,5*S*)-2 except that D-Ala was used instead of L-Ala: yield, 71.6%; TLC R_f = 0.50 (A), 0.18 (B), 0.01 (C); $[\alpha]^{25}_D$ = −31.8° (*c* = 1.07, CH_2Cl_2); mp = 168–171 °C; ^1H NMR ($CDCl_3$) δ 7.62–7.37 (5H, m), 5.65 (s, 1H), 4.24 (q, 1H, *J* = 6.7 Hz), 3.05 (s, 3H), 1.05 (s, 9H), 0.86 (d, 3H, *J* = 6.5 Hz).

Mixture of (2*R*,5*R*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*R*)-methylbenzyl)imidolazolidin-4-one ((2*R*,5*R*,5-α*R*)-3) and (2*R*,5*R*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*S*)-methylbenzyl)imidazolidin-4-one ((2*R*,5*R*,5-α*S*)-3). This was obtained from (2*R*,5*R*)-2 as above to yield 13.9 g (65.4%) after chromatographic purification (5-α*R*/5-α*S*, 1:3, respectively, by NMR). The diastereoisomers could be separated by a single crystallization from EtOAc/petroleum ether.

(2*R*,5*R*,5-α*R*)-3. The ^1H NMR is identical to that of (2*S*,5*S*,5-α*S*)-3; $[\alpha]^{25}_D$ = 95.1° (*c* = 0.545, $CHCl_3$); MS $(M + 1)_{calcd}$ = 379, $(M + 1)_{found}$ = 379; TLC R_f = 0.66 (A), 0.43 (B), 0.08 (C); mp = 130–133 °C.

(2*R*,5*R*,5-α)-3. The ^1H NMR of is identical to that of (2*S*,5*S*,5-α*R*)-3; $[\alpha]^{25}_D$ = −37.7° (*c* = 0.515, $CHCl_3$); MS $(M + 1)_{calcd}$ = 379, $(M + 1)_{found}$ = 379; TLC R_f = 0.66 (A), 0.43 (B), 0.08 (C); mp = 127–129 °C.

(2*R*,5*R*)-1-Benzoyl-2-*tert*-butyl-3-methyl-5-(α(*S*)-methylbenzyl)imidazolidin-4-one ((2*R*,5*R*,5-α*S*)-3). The preparation of the title compound was accomplished as above with a 3-fold excess of (1-bromoethyl)benzene for a 10-h reaction time; yield, 83.4%.

Preparation of (2*R*,3*R*)-2,3-dimethylphenylalanine ((2*R*,3*R*)-4. The title compound was synthesized as for ((2*S*,3*S*)-4 in a yield of 82.4%: ^1H NMR δ 7.08 (m, 5H), 3.05 (q, 7.4 Hz, 1H), 1.14 (s, 3H), 1.11 (d, 7.4 Hz, 3H); ^{13}C NMR: 178.20, 140.50, 128.55, 128.52, 127.51, 127.51, 63.32, 44.77, 19.33, 13.75; MS (CI with isobutane) $(M + 1)_{calcd}$ = 194, $(M + 1)_{found}$ = 194; $[\alpha]^{25}_D$ = +33.3° (*c* = 0.450, MeOH). Anal. Calcd C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40; H, 7.66; N, 7.02 .

(2*R*,3*S*)-2,3-Dimethylphenylalanine ((2*R*,3*S*)-4). The title compound was synthesized from (2*R*,3*R*,5-α*S*)-3; yield, 73.4%; ^1H NMR δ 7.09 (m, 5H), 2.96 (q, 7.3 Hz, 1H), 1.05 (d, 7.3 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR δ 179.60, 140.60, 129.02, 128.34, 127.24, 63.09, 45.66, 23.08, 14.89; MS (CI with isobutane) $(M + 1)_{calcd}$ = 194, $(M + 1)_{found}$ = 194; $[\alpha]^{25}_D$ = −20.5° (*c* = 0.480, MeOH). Anal. Calcd C, 68.37, H, 7.82, N, 7.25. Found: C, 68.40, H, 7.43, N, 7.38.

***N*-Methyl-3(*R*),(4*R*)-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*R*,4*R*)-5).** The title compound was synthesized from (2*R*,3*R*)-4 as described for (3*S*,4*R*)-5 in a yield of 87.3%: ^1H NMR δ 7.02 (m, 4H), 4.01 (d, 1H, 16.7 Hz), 3.81 (d, 1H, 16.7 Hz) 3.19 (q, 1H, 7.0 Hz), 2.40 (s, 3H), 0.99 (d, 3H, 7.1 Hz), 0.85 (s, 3H); ^{13}C NMR δ 176.30, 135.80, 128.80, 127.67, 125.68, 125.49, 70.10, 51.98, 39.04, 38.37, 13.65, 7.57; MS (CI with isobutane) $(M + 1)_{calcd}$ = 220, $(M + 1)_{found}$ = 220; other MS fragments found, 204 $(M - CH_3)$, 174 (M − COOH); $[\alpha]^{25}_D$ = +46.8° (*c* = 0.483, MeOH).

(3*R*,4*S*)-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*S*,4*R*)-5). The title compound was synthesized from (2*R*,3*S*)-4 as described: yield 83.5%; ^1H NMR δ 7.04 (m, 4H), 4.03 (d, 1H, 18.0 Hz), 3.91 (d, 1H, 18.0 Hz), 2.82 (q, 1H, 7.2 Hz), 1.10 (s, 3H), 0.91 (d, 3H, 7.2 Hz); ^{13}C NMR δ 178.10, 137.70, 129.83, 128.82, 127.49, 126.69, 125.97, 62.97, 41.32, 38.76, 19.59, 19.51; MS (CI with isobutane) $(M + 1)_{calcd}$ = 206, $(M + 1)_{found}$ = 206; $[\alpha]^{25}_D$ = +90.9° (*c* = 0.486, MeOH). Anal. Calcd C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.41; N, 6.67.

(3*R*,4*R*)-3,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((3*R*,4*R*)-6). The title compound was synthesized from (2*R*,3*R*)-4, analogously to the procedure established above, in a yield of 76.3%.

Proof of the Optical Purity of the Amino Acids. Both (2*R*,3*S*)-4 and (3*R*,4*S*)-5 were converted to their methyl esters (2*R*,3*S*)-7 and (3*R*,4*S*)-9, respectively, by $SOCl_2$ in CH_3OH. The pure esters were reacted with (−)-(*S*)-α-methylbenzyl isocyanate (Aldrich) in $CDCl_3$ in presence of the catalytic amounts of DMAP to form (2*R*,3*S*)-8 and (3*R*,4*S*)-10, respectively.

(2*R*,3*S*)-7: ^1H NMR ($CDCl_3$) δ 7.23 (m, 5H), 3.71 (s, 3H), 3.11 (q, 1H, 7.2 Hz), 1.24 (d, 3H, 7.1 Hz), 1.14 (s, 3H).

(2*R*,3*S*)-8: ^1H NMR ($CDCl_3$) δ 7.20 (m, 18H, contains aromatic protons of the urea and excess of isocyanate), 5.14 (s, 1H, NH of urea, from the amino acid), 5.03 (d, 7.0 Hz, 1H, NH of urea, from the isocyanate), 4.73 (q, 1H, α-benzylic of urea from the isocyanate), 4.72 (q, α-H of excess isocyanate), 3.53 (s, 3H, OMe),

3.35 (q, 1H, 7.0 Hz, CH_β of urea, amino acid part), 1.57 (s, 3H, Me from the urea, amino acid part), 1.57 (d, Me from excess isocyanate), 1.40 (d, 3H, 7.0 Hz, urea, from the isocyanate), 1.25 (d, 3H, 7.0 Hz, urea, from the amino acid).

(3*R*,4*S*)-9: ^{1}H NMR δ 7.10 (m, 4H), 4.09 (s, 2H), 3.77 (s, 3H), 2.92 (q, 1H, 7.0 Hz), 2.15 (broad, 1H), 1.36 (s, 3H), 1.11 (d, 3H, 7.0 Hz).

(3*R*,4*S*)-10: ^{1}H NMR δ 7.30 (m, 9H + free isocyanate), 5.00 (dq, 1H, 7.0 Hz, 7.0 Hz), 4.76 (q, 1H, 6.7 Hz), 4.78 (d, 1H), 4.60 (d, 1H, 13.8 Hz, N-CH), 4.37 (d, 1H, 13.8 Hz, N-CH), 3.50 (s, 3H), 1.58 (d, 3H, 6.7 Hz), 1.54 (s, 3H), 1.51 (d, 6.8 Hz, 3H), 1.17 (d, 7.1 Hz, 3H)

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