Pergamon

Tetrahedron 56 (2000) 5479–5492

TETRAHEDRON

A Convenient Synthesis of Conformationally Constrained β-Substituted Tryptophans

Csaba Nemes,[†] Laurent Jeannin,[‡] Janos Sapi, Marie Laronze, Houria Seghir, Franck Augé and Jean-Yves Laronze*

UPRES A CNRS 6013 'Isolement, Structure, Transformations et Synthèse de Produits Naturels', IFR 53 Biomolécules, Faculté de Pharmacie, Université de Reims-Champagne-Ardenne, 51, rue Cognacq-Jay, F-51096 Reims Cedex, France

Received 6 March 2000; accepted 25 May 2000

Abstract—A short and general synthesis for the preparation of various conformationally constrained β-substituted tryptophans has been elaborated starting from indole, aldehydes and Meldrum's acid by using trimolecular condensation and Curtius rearrangement mediated functional group transformations followed by deprotections, as key-steps. The relative configurations of the two diastereomeric series have been determined indirectly by the measurement of ^3J coupling constants in the corresponding tetrahydro-β-carbolines, and further supported by means of molecular modelizations.

Introduction

Replacement of amino acids by their conformationally constrained non-natural analogs in peptides has become a versatile tool in the study of peptide–receptor relationships.[1] The relatively good correlation found between the conformational properties of individual amino acid residues and the secondary structure of peptides[2] containing them has stimulated molecular modeling studies, conformational analyses, rational design and synthetic efforts of such non-natural amino acids.[3]

Among the proteinogenic α-amino acids subjected to structural modifications tryptophan occupies a special position owing to its presence in various biologically active peptides,[4] as well as due to detailed conformational studies of β-methyl(phenyl)tryptophan isomers. For example, in the frame of the refinement of structure–activity relationships, incorporation of the four β-methyltryptophan isomers of different conformational profile revealed how topographical modifications of peptides were able to influence ligand–receptor interactions leading to significant differences in potency and selectivity.[5] Finally, the simplest β-substituted analog, the β-methyltryptophan core is also present in some natural products, such as the antimicrobial telomycine,[6] the antimicrobial and antitumoral streptonigrine,[7] or the antitumoral alkaloid lavendamycine.[8]

Since the pioneering work of Snyder[9] on the synthesis of β-methyltryptophan, synthetic efforts for the preparation of other β-substituted tryptophans have been stimulated by medicinal and/or natural product chemistry applications. Later on, Snyder's first 'gramine chemistry' method was improved by using nitroacetates as nucleophiles[10] allowing the preparation of structurally diversified β-substituted tryptophan analogs implied in the synthesis of β-carboline derivatives.[11] Other improvements,[12] including the development of enantioselective versions[13] have also been achieved, mainly for the preparation of β-methyltryptophans, by using chiral auxiliaries[13a] and/or organocuprates,[13a,b] however, these methods also required indole nitrogen protections. Recently, novel approaches have been described for the synthesis of β,β-cyclized tryptophans,[14] β-trifluoromethyl-*N*-acetyl-,[15] and other β-substituted tryptophan derivatives.[16] Nonetheless, despite the numerous efforts outlined above, a general and convenient procedure leading to structurally diversified β-substituted tryptophans still remained a challenge.

Results and Discussion

In order to keep up with this challenge, we have elaborated a novel method[17] based on an entirely different approach towards β-substituted tryptophan derivatives from those known in the literature. Herein we disclose this general method in full detail with some refinements compared to

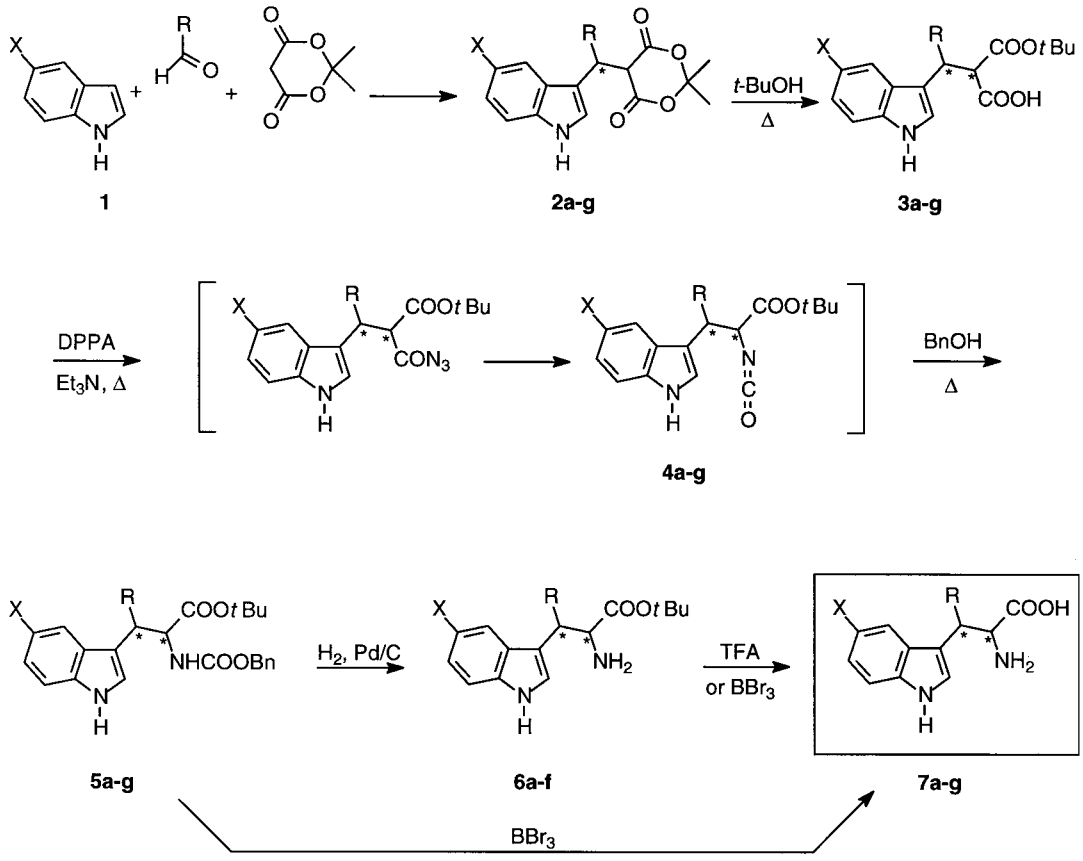
Keywords: β-substituted tryptophan; constrained conformation; Meldrum's acid.

* Corresponding author. Tel.: +33-326-913589; fax: +33-326-918025; e-mail: jy.laronze@univ-reims.fr

[†] 'Maître des conférences associé' at the Université de Reims Champagne-Ardenne (1996–1999); present address: The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

[‡] Present address: Peptisyntha RD, B-1120 Bruxelles, Belgium.

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00446-4



2-7	a	b	c	d	e	f	g
X	H	H	H	H	H	H	Br
R	Me	*i*-Pr	3-pentyl	Chx	Ph	2,5-diOMePh	Me

Chx : cyclohexyl; 2,5-diOMePh : 2,5-dimethoxyphenyl

Scheme 1.

the preliminary version, leading to various conformationally constrained β-substituted tryptophans. Our strategy is based on selective functional group transformations on the Meldrum's acid core of the trimolecular adducts, as depicted in Scheme 1.

In the first step the trimolecular condensation of unprotected indoles **1** with various aldehydes and Meldrum's acid,[18] according to Yonemitsu conditions,[19] smoothly gave adducts **2** in high yields. The unique 1,3-dioxane-4,6-dione appendage of adducts **2** seemed to be convenient for further functional group transformations, as by alcoholysis it could be transformed into hemiacid esters **3**. The ester function of these latter could be regarded as the esterified acid functionality of a tryptophan, while the carboxylic group could be transformed into an amino group.

Accordingly, treatment of adducts **2** with *tert*-butanol afforded hemiacid esters **3** as a mixture of diastereomers. Since for structure–activity relationship studies in peptides all diastereomeric β-substituted tryptophans were needed, it was useless to continue to seek by all means for diastereoselectivity. Otherwise, examination of Dreiding models showed that only low diastereoselectivity,[20] if any, could be achieved during the ring opening (maximum d.e. 40% for **3f**). It is worth noting that these reactions should be carried out carefully, due to the potential decarboxylation of hemiacid esters **3** formed.

For the transformation of hemiacid esters **3** into carbamates **5** the classical Curtius rearrangement mediated one-pot procedure has been envisaged. Treatment of hemiacid esters **3** with diphenylphosphoryl azide (DPPA[21]) led to the corresponding acylazides, which were subjected to a Curtius rearrangement to afford isocyanates **4**. Isocyanate intermediates **4** were then transformed into carbamate esters **5** by the addition of benzyl alcohol to obtain the latter in high yields. At this phase we tried to separate the diastereomers of carbamate esters **5**, which was successful for compounds **5a**, **5b** and **5g**. We have to note that from this point in our reaction sequence, a different route from the one detailed below could be followed in favor of peptide chemistry applications. Namely, the *tert*-butyl ester function of carbamate esters **5** can be selectively cleaved, and the resulting *Z*-protected amino acids could be useful in peptide syntheses.

The fourth step of our synthesis consists of the debenzylation of carbamate esters **5** by catalytic hydrogenation to afford amino esters **6**. We had to do this reaction for two reasons. On the one hand, we could separate the formerly unseparable diastereomers at the amino ester phase in the case of **6c**, **6e** and **6f**, but unfortunately, we did not succeed with amino ester **6d**. On the other hand, however, it was necessary to have amino esters **6** for the determination of the relative configuration of the diastereomers.

For the final deprotection of *tert*-butyl esters **6** the well-known trifluoroacetic acid assisted method could be proposed, but we preferred using boron tribromide, since by this method both the carbamate and the ester functions could be simultaneously cleaved. Thus, diastereomerically pure carbamate esters **5** (except for the unseparable **5d**, R: cyclohexyl) or amino esters **6** (except for **6f**) were treated with 1 M boron tribromide solution in dichloromethane to afford the appropriate β-substituted tryptophans **7**, as hydrobromide salts, in almost quantitative yields. As for the exceptions, β-cyclohexyl tryptophan **7d** was obtained as a diastereomeric mixture, while in the case of amino ester **6f** we had to apply trifluoroacetic acid for the deprotection, as with boron tribromide *O*-demethylation also took place.

Relative configuration determination

In order to determine the relative configuration of the diastereomers, we performed a Pictet–Spengler cyclization on amino esters **6** with cyclohexanone to afford tetrahydro-β-carbolines **8** (Table 1). In these cyclizations from one series of diastereomers we should get *cis*-tetrahydro-β-carbolines, while the other series should afford *trans*-tetrahydro-β-carbolines. Formerly we applied[22] the same Pictet–Spengler cyclization with cyclohexanone for the synthesis of tetrahydro-β-carbolines, in the presence of acetic acid. In our present study, however, the use of the same method turned out to be problematic. We noticed that in most cases the application of acetic acid led to epimerization on the C-3 center, which rendered the configuration assignment unreliable. Finally, after several attempts to utilize various acids in various quantities, we found that the most advantageous way was to add no acid to the solutions of amino esters **6** and cyclohexanone in refluxing dry toluene. With this method, although the reactions sometimes became considerably slower, we could avoid the undesired epimerization.

The determination of the relative configurations is based on the measurement of the coupling constant values between the protons at positions 3 and 4 of the tetrahydro-β-carboline ring. As shown in Table 1, the coupling constants obtained are in good accordance with the expected values ($^3J_{trans}$=9–10 Hz, $^3J_{cis}$=3–4.5 Hz), nevertheless, the relatively low $^3J_{trans}$ couplings for tetrahydro-β-carbolines **8b**,**c** suggested us that we should seek further evidence to this configuration assignment by molecular modelizations.

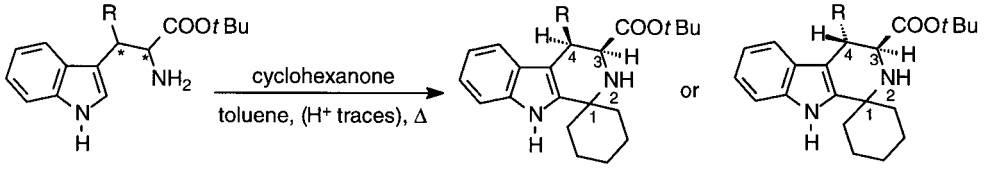
Computational methods and results[23]

The coupling constant values between protons 3-H and 4-H of tetrahydro-β-carbolines **8** were determined for both enantiomeric pairs of each compound by following the protocol below [the calculations were executed on a Silicon Graphics Octane (R10000/225 MHz) computer].

Conformational analysis. By means of exploring the potential energy surface for each molecule, we performed a conformational analysis using a combined method of molecular dynamics simulations and minimizations. For this purpose, we utilized the DISCOVER®[24] program with the CFF91[25] forcefield by MSI. Of the numerous conformations obtained we kept those with the lowest energies, in an interval of 40 kJ.

Quantumchemical minimizations. On the sample of conformers selected in the previous step, we carried out a second energy minimization by means of semiempirical AM1[26] calculations with the GAUSSIAN98[27] program. These computations allowed us to have a better energy classification of the conformers, of which we now kept those of the lowest energies, in an interval of 10 kJ.

Table 1. Determination of the relative configuration of the diastereomers: Pictet–Spengler cyclization of amino esters **6** to tetrahydro-β-carbolines **8**



6a-f *cis*-**8** *trans*-**8**

Tetrahydro-β-carboline	R	Reaction time (h)	Yield (%)	$^3J_{exp}$ (Hz)	$^3J_{th}$ (Hz)
cis-(3*S**,4*R**)-**8a**	Me	3.5	90	4.0	2.5
trans-(3*S**,4*S**)-**8a**		24	63	9.4	10.7
cis-(3*S**,4*R**)-**8b**	*i*-Pr	1.5	90	3.5	2.7
trans-(3*S**,4*S**)-**8b**		8	65	5.8	6.2
cis-(3*S**,4*R**)-**8c**	3-pentyl	5	98	3.8	4.2
trans-(3*S**,4*S**)-**8c**		4.5	71	6.6	5.7
cis-(3*S**,4*R**)-**8e**	Ph	10	90	4.5	2.4
trans-(3*S**,4*S**)-**8e**		7	89	9.8	9.4
cis-(3*S**,4*S**)-**8f**	2,5-diOMe-Ph	7	88	4.8	2.5
trans-(3*S**,4*R**)-**8f**		5	85	9.1	7.0

Calculation of the coupling constants ^3J_i. For each conformer i selected, we calculated the coupling constant values between protons 3-H and 4-H of tetrahydro-β-carbolines **8**. For this purpose we used the GEOMOS[28] program.

Calculation of the global theoretical coupling constant values $^3J_{th}$. On the basis of the previous computations, by knowing the statistical occurence of each conformer in the sample and its coupling constant value ^3J_i, it was possible to determine the global coupling constant value $^3J_{th}$.

The experimental ($^3J_{exp}$) and the theoretical ($^3J_{th}$) coupling constant values are shown in Table 1. It can be seen that the two values for the same diastereomeric racemates are in good coherence with one another. To our contentment, the best results were obtained in the case of tetrahydro-β-carbolines **8b**,**c**, for which compounds we were not totally certain about our configuration assignment, due to the relatively low difference between the respective experimental $^3J_{trans}$ and $^3J_{cis}$ values.

Despite the slight discrepancies, these results are rather satisfactory, and the good accordance between the experimental and theoretical coupling constant values permits the differentiation between the *trans* and *cis* isomers with no ambiguity, giving credence to our configuration assignment.

Conclusion

In summary, we have developed a short, convenient procedure for the preparation of various conformationally constrained β-substituted tryptophans which, after convenient protections depending on the coupling strategy to be used, and resolution,[29] could be incorporated into divers peptides as well as used in combinatorial libraries. Additionally, the spatially well-defined β-substitution patterns would be of great value for further conformational property studies by means of the explorations of χ-space[3b] and other intramolecular interactions (hydrogen bonding, van der Waals, etc.). Both synthetic applications and conformational analyses of β-substituted tryptophans **7** are in progress.

Experimental

Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. IR spectra were measured with a BOMEM FTIR instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Brucker AC 300 spectrometer using TMS as internal standard. Mass spectra were recorded with VG Autospec (EI, 70 eV) and Finnigen TSQ 700 (ESI) apparatuses. All solvents were purified by following standard literature methods. Column chromatography was performed on Kieselgel 60 (0.063–0.200 mm, Merck). Separations with Chromatotron® or on preparative TLC plates were effected on Kieselgel 60 PF_{254} (Merck). Reactions were monitored using Merck TLC aluminium sheets (Kieselgel 60 F_{254}).

General procedure for the trimolecular condensation of indoles 1 with aldehydes and Meldrum's acid

To a solution of indole **1** (2.50–5.00 g, 15.3–42.7 mmol) and Meldrum's acid (2.65–6.15 g, 18.4–42.7 mmol, 1.0–1.2 equiv.) in MeCN (30–50 mL) distilled aldehyde (42.4–85.4 mmol, 1.0–3.0 equiv.) and a catalytic amount of D,L-proline (0.05 equiv.) were added. After stirring at room temperature for 6–24 h, the solvent was evaporated under reduced pressure and the residue was purified by crystallization or by column chromatography to give the corresponding adducts **2a**–**g**.

5-[1-(Indol-3-yl)-ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2a). From indole: 5.00 g (42.7 mmol), Meldrum's acid: 6.15 g (42.7 mmol), acetaldehyde: 3.75 g (85.4 mmol), MeCN: 50 mL, stirring: 16 h, crystallization: ether. Yield: 10.18 g (83%); mp 130–132°C; IR (KBr) 3414, 3057, 1778, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, s), 1.57 (3H, s), 1.64 (3H, d, J=7.8 Hz), 3.80 (1H, d, J=2.9 Hz), 4.34 (1H, dq, J=7.8, 2.9 Hz), 7.05–7.19 (3H, m), 7.28 (1H, dd, J=8.1, 1.0 Hz), 7.63 (1H, dd, J=8.1, 1.0 Hz), 8.30 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 18.1, 27.5, 27.9, 31.0, 51.4, 104.9, 111.2, 116.1, 118.4, 119.5, 121.9, 123.3, 126.1, 135.6, 165.2, 165.5; MS (EI) *m/z* 287 (M^+), 170, 144; HRMS calcd for $C_{16}H_{17}NO_4$ 287.1158. Found 287.1178. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.16; H, 5.67; N, 5.07.

5-[1-(Indol-3-yl)-2-methylpropyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2b). From indole: 5.00 g (42.7 mmol), Meldrum's acid: 6.15 g (42.7 mmol), isobutyraldehyde: 6.16 g (85.4 mmol), MeCN: 50 mL, stirring: 24 h, crystallization: hexane/ether 1:1. Yield: 10.36 g (77%); mp 130–131°C; IR (KBr) 3414, 2965, 1738, 1292 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, J=5.9 Hz), 1.08 (3H, s), 1.19 (3H, d, J=5.9 Hz), 1.58 (3H, s), 2.78 (1H, m), 3.76 (1H, brd, J=11.3 Hz), 3.92 (1H, brs), 7.00–7.22 (3H, m), 7.32 (1H, d, J=7.7 Hz), 7.70 (1H, d, J=7.7 Hz), 8.21 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.8, 27.9, 28.2, 30.8, 48.8, 105.2, 110.9, 115.1, 119.5, 119.8, 122.2, 123.1, 127.3, 135.5, 165.8, 166.6; MS (EI) *m/z* 315 (M^+), 172, 170; HRMS calcd for $C_{18}H_{21}NO_4$ 315.1471. Found 315.1475. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.43; H, 7.02; N, 4.50.

5-[2-Ethyl-1-(indol-3-yl)-butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2c). From indole: 5.00 g (42.7 mmol), Meldrum's acid: 6.15 g (42.7 mmol), 2-ethylbutyraldehyde: 8.54 g (85.4 mmol), MeCN: 50 mL, stirring: 16 h, crystallization: hexane/CH_2Cl_2, 4:1. Yield: 12.01 g (82%); mp 128–129°C; IR (film) 3414, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70 (3H, t, J=7.0 Hz), 0.87 (3H, s), 1.00 (3H, t, J=7.0 Hz), 1.11 (2H, m), 1.30 (2H, m), 1.45 (3H, s), 2.50 (1H, m), 3.70 (1H, d, J=3.0 Hz), 4.00 (1H, dd, J=11.1, 3.0 Hz), 7.00–7.20 (5H, m), 8.20 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 8.6, 9.9, 21.4, 21.6, 27.6, 28.1, 40.4, 40.6, 48.1, 105.2, 110.9, 114.7, 119.3, 119.6, 121.3, 121.9, 127.2, 135.4, 165.6, 167.0; MS (EI) *m/z* 287, 245, 199; HRMS calcd for $C_{20}H_{25}NO_4$ 343.1784. Found: 343.1788. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.03; H, 7.26; N, 3.91.

5-[Cyclohexyl-(indol-3-yl)-methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2d). From indole: 2.50 g (21.4 mmol), Meldrum's acid: 3.38 g (23.5 mmol), cyclohexanecarboxaldehyde: 5.46 g (47.1 mmol), MeCN: 30 mL, stirring: 6 h, chromatography: CH_2Cl_2/MeOH 99:1. Yield: 5.69 g (75%); viscous oil; IR (film) 3414, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3H, s), 1.10–1.42 (5H, m), 1.52 (3H, s), 1.61–2.05 (5H, m), 2.40 (1H, m), 3.88 (1H, dd, J=11.4, 2.7 Hz), 4.02 (1H, d, J=2.7 Hz), 7.08–7.20 (3H, m), 7.35 (1H, d, J=8.6 Hz), 7.72 (1H, d, J=8.6 Hz), 8.15 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 25.6, 26.0, 27.2, 27.6, 31.7, 39.6, 43.1, 47.8, 105.0, 110.9, 114.8, 119.1, 119.3, 121.7, 123.0, 127.2, 135.3, 165.7, 166.5; MS (EI) m/z 355 (M^+), 212, 170, 130. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.21; H, 7.26; N, 3.90.

5-[(Indol-3-yl)-phenylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2e). From indole: 5.00 g (42.7 mmol), Meldrum's acid: 6.15 g (42.7 mmol), benzaldehyde: 9.05 g (85.4 mmol), MeCN: 50 mL, stirring: 16 h, crystallization: ether. Yield: 14.14 g (95%); mp 175–176°C; IR (KBr) 3404, 3140, 1780, 1749 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.57 (3H, s), 1.84 (3H, s), 5.20 (1H, brs), 5.52 (1H, brs), 6.95 (1H, t, J=8.2 Hz), 7.10 (1H, t, J=8.2 Hz), 7.15–7.50 (8H, m), 10.97 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 26.7, 27.9, 40.2, 51.8, 105.1, 111.6, 113.4, 118.7, 118.8, 121.3, 124.2, 126.5, 127.9, 128.4, 129.0, 136.0, 141.4, 165.2, 165.7; MS (EI) m/z 349 (M^+), 247, 206, 174; HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314. Found: 349.1323. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.80; H, 5.27; N, 3.91.

5-[(2,5-Dimethoxyphenyl)-(indol-3-yl)-methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2f). From indole: 5.00 g (42.7 mmol), Meldrum's acid: 6.15 g (42.7 mmol), 2,5-dimethoxybenzaldehyde: 7.10 g (42.7 mmol), MeCN: 50 mL, stirring: 15 h, crystallization: ether. Yield: 15.01 g (86%); mp 138–139°C; IR (KBr) 3401, 2947, 1782, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3H, s), 1.65 (3H, s), 3.55 (3H, s), 3.85 (3H, s), 4.46 (1H, d, J=3.4 Hz), 5.76 (1H, d, J=3.4 Hz), 6.67–6.82 (3H, m), 7.04 (1H, t, J=8.2 Hz), 7.12 (1H, t, J=8.2 Hz), 7.23 (1H, d, J=2.7 Hz), 7.28 (1H, d, J=8.2 Hz), 7.52 (1H, d, J=8.2 Hz), 8.32 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.5, 28.1, 35.7, 50.6, 55.2, 55.6, 104.6, 110.6, 111.1, 111.6, 114.3, 118.2, 119.0, 119.5, 122.2, 123.7, 127.3, 129.7, 135.8, 150.6, 153.3, 165.0, 165.6; MS (EI) m/z 409 (M^+), 323, 307, 292; 279, 266; HRMS calcd for $C_{23}H_{23}NO_6$ 409.1525. Found: 409.1543. Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.10; H, 5.49; N, 3.38.

5-[1-(5-Bromoindol-3-yl)-ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2g). From 5-bromoindole: 3.00 g (15.3 mmol), Meldrum's acid: 2.64 g (18.36 mmol), acetaldehyde: 2.02 g (45.9 mmol), MeCN: 40 mL, stirring: 12 h, chromatography: hexane/acetone 8:2. Yield: 4.21 g (75%); viscous oil; IR (film) 3416, 2944, 1761, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3H, s), 1.65 (3H, d, J=7.3 Hz), 1.70 (3H, s), 3.79 (1H, d, J=2.7 Hz), 4.27 (1H, dq, J=2.7, 7.3 Hz), 7.18–7.30 (3H, m), 7.79 (1H, s), 8.50 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 17.9, 27.5, 28.3, 30.5, 51.4, 104.9, 112.7, 112.9, 116.1, 121.1, 124.9, 125.5, 128.1, 134.2, 164.7, 165.4; MS (EI) m/z 367/365 (M^+), 281/279, 265/263, 224/222. Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82. Found: C, 52.19; H, 4.48; N, 3.76.

General procedure for the preparation of hemiacid esters 3a–g

Adducts **2a–g** (0.300–10.19 g, 0.86–29.2 mmol) were dissolved in a mixture of pyridine (1–27 mL) and the appropriate dry alcohol (5–100 mL), and were heated under reflux for 1–3 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2, then washed at 0°C with 5% citric acid and water. The organic phase was dried over $MgSO_4$ and evaporated to dryness. Crystallization or column chromatography of the residue gave hemiacid esters **3a–g** as diastereomeric mixtures.[30]

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-(indol-3-yl)-butyric acid (3a).** From **2a**: 4.02 g (14.0 mmol), pyridine: 15 mL, *tert*-butyl alcohol: 60 mL, reflux: 1.5 h, chromatography: CH_2Cl_2/MeOH 98:2. Yield: 3.51 g (83%); viscous oil; IR (film) 3412, 2978, 1724 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (1.41) (9H, s), 1.43 (3H, d, J=7.2 Hz), 3.80 (2H, m), 6.86 (1H, m), 7.00–7.15 (2H, m), 7.23 (1H, t, J=7.9 Hz), 7.62 (1H, d, J=7.9 Hz), 8.28 (8.32) (1H, brs), 9.41 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 19.1 (19.9), (27.1) 27.6, 31.8 (32.2), 58.8 (59.3), (82.1) 82.5, (111.2) 111.3, (116.8) 117.1, 118.8 (118.8), 118.9 (118.9), (119.0) 119.1, (121.6) 121.8, 126.0 (126.1), 136.1 (136.1), 168.3 (168.4), 173.4 (173.5) (Signals in brackets belong to the same diastereomer); MS (EI) m/z 303 (M^+), 245, 224; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471. Found: 303.1469. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.06; H, 6.90; N, 4.65.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-(indol-3-yl)-4-methylpentanoic acid (3b).** From **2b**: 9.20 g (29.2 mmol), pyridine: 18 mL, *tert*-butyl alcohol: 60 mL, reflux: 1 h, crystallization: hexane/ether 3:2. Yield: 7.91 g (82%); mp 171–173°C; IR (KBr) 3437, 2968, 1740, 1686 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.78 (3H, d, J=5.9 Hz), 0.83 (3H, d, J=5.9 Hz), 0.89 (9H, s), 2.03 (1H, m), 3.58–3.68 (1H, m), 3.73–3.83 (1H, m), 6.98 (1H, t, J=7.7 Hz), 7.05 (1H, t, J=7.7 Hz), 7.12 (7.19) (1H, brs), 7.32 (1H, d, J=7.7 Hz), 7.57 (1H, d, J=7.7 Hz), 10.90 (1H, brs), 12.70 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 17.4 (17.4), 22.2 (22.3), 27.0 (27.7), 29.9 (29.9), (41.2) 41.4, (57.2) 57.5, 80.1 (81.1), 111.3 (111.3), 111.5 (111.8), 118.3 (118.4), (119.2) 119.3, 120.7 (120.7), (123.7) 124.0, 128.8 (128.8), 135.8 (135.8), 167.3 (168.2), (169.4) 170.3 (Signals in brackets belong to the same diastereomer); MS (EI) m/z 331 (M^+), 188, 172, 170; HRMS calcd for $C_{19}H_{25}NO_4$ 331.1784. Found: 331.1810. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.22. Found: C, 69.10; H, 7.63; N, 4.15.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-4-ethyl-3-(indol-3-yl)-hexanoic acid (3c).** From **2c**: 10.02 g (29.2 mmol), pyridine: 18 mL, *tert*-butyl alcohol: 60 mL, reflux: 1.5 h, crystallization: hexane/ether 1:2. Yield: 7.26 g (69%); mp 180–181°C; IR (KBr) 3441, 2967, 1734, 1713 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85 (3H, t,

J=6.8 Hz), 0.90 (1.45) (9H, s), 1.02 (3H, t, J=6.8 Hz), 1.26 (2H, m), 1.40 (1H, m), 1.68 (2H, m), 3.78–3.90 (2H, m), 6.99 (1H, t, J=7.7 Hz), 7.05 (1H, t, J=7.7 Hz), 7.14 (7.19) (1H, brs), 7.32 (1H, d, J=7.7 Hz), 7.55 (1H, d, J=7.7 Hz), 10.88 (1H, brs), 12.48 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 12.5 (12.5), 12.7 (12.7), 22.9 (22.9), 23.9 (23.9), 27.1 (27.7), (37.4) 37.7, 44.4 (44.4), 57.6 (57.6), 80.0 (81.5), 111.3 (111.3), 112.2 (113.0), 118.3 (118.4), (118.9) 119.0, 120.7 (120.7), (123.5) 123.9, 128.8 (128.8), 135.7 (135.7), 167.4 (168.1), (169.3) 170.2 (Signals in brackets belong to the same diastereomer); MS (EI) m/z 359 (M^+), 200, 188, 170; HRMS calcd for $C_{21}H_{29}NO_4$ 359.2097. Found: 359.2100. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.01; H, 7.96; N, 3.85.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-cyclohexyl-3-(indol-3-yl)-propionic acid (3d).** From **2d**: 10.19 g (28.7 mmol), pyridine: 27 mL, *tert*-butyl alcohol: 100 mL, reflux: 2 h, chromatography: CH_2Cl_2/MeOH 95:5, then crystallization: ether. Yield: 8.92 g (84%); mp 114–116°C; IR (KBr) 3412, 2928, 1720, 1705 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.63–1.28 (5H, m) 1.43 (9H, brs), 1.50–1.84 (6H, m), 3.56–3.71 (1H, m), 3.81–3.95 (1H, m), 6.93–7.10 (2H, m), 7.18 (1H, brs), 7.30 (1H, d, J=8.7 Hz), 7.55 (1H, d, J=8.7 Hz), 10.90 (1H, brs), 12.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 26.1 (26.1), 26.5 (26.5), 27.1 (27.7), 32.4 (32.5), 40.6 (40.6), 41.3 (41.3), 56.6 (56.7), (80.1) 81.1, 111.3 (111.3), (112.5) 112.9, (118.3) 118.4, (119.2) 119.3, 120.7 (120.7), 123.5 (123.7), 128.7 (128.7), 135.8 (135.8), (167.5) 168.4, 169.5 (170.4) (Signals in brackets belong to the same diastereomer); MS (EI) m/z 371 (M^+), 271, 243, 212, 188, 170; HRMS calcd for $C_{22}H_{29}NO_4$ 371.2097. Found: 371.2110. Anal. Calcd for $C_{22}H_{29}NO_4 \cdot 0.5H_2O$: C, 69.45; H, 7.95; N, 3.68. Found: C, 69.35; H, 7.69; N, 3.65.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-(indol-3-yl)-3-phenylpropionic acid (3e).** From **2e**: 4.89 g (14.0 mmol), pyridine: 15 mL, *tert*-butyl alcohol: 60 mL, reflux: 1.5 h, crystallization: ether. Yield: 3.63 g (71%); mp 180–182°C; IR (KBr) 3437, 3412, 3133, 1724 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.16 (1.19) (9H, s), 4.20 (4.25) [1H, d, J=6.2 (7.1) Hz], 4.84 (4.88) [1H, d, J=6.2 (7.1) Hz], 6.98–7.55 (10H, m), 10.67 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 27.3 (27.3), 42.3 (42.6), 58.4 (58.5), 80.7 (80.8), 111.2 (111.2), 115.9 (116.4), 118.4 (118.6), 120.9 (121.0), (121.1) 121.4, 126.0 (126.1), 126.4 (126.5), 127.5 (127.8), 127.9 (128.0), 128.1 (128.3), (136.1) 136.2, 142.1 (142.6), 166.9 (167.0), (169.1) 169.2 (Signals in brackets belong to the same diastereomer); MS (EI) m/z 365 (M^+), 264, 246, 219, 205; HRMS calcd for $C_{22}H_{23}NO_4$ 365.1627. Found: 365.1608. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.28; H, 6.14; N, 4.07.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-(2,5-dimethoxyphenyl)-3-(indol-3-yl)-propionic acid (3f).** From **2f**: 5.72 g (14.0 mmol), pyridine: 15 mL, *tert*-butyl alcohol: 60 mL, reflux: 1.5 h, crystallization: ether. Yield: 5.73 g (96%); mp 164–166°C; IR (KBr) 3337, 3144, 3086, 1739, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 1.03 (1.12) (9H, s), 3.53 (3.70) (3H, s), 3.64 (3.80) (3H, s), 4.21 (4.43) (1H, d, J=11.4 Hz), 5.18 (5.32) (1H, d, J=11.4 Hz), (6.44) 6.73 [1H, d, J=(3.1) 3.1 Hz], 6.45 (6.60) [1H, dd, J=7.9, 3.1 (8.0, 3.1) Hz], 6.55 (6.72) [1H, d, J=7.9 (8.0) Hz], 6.80 (7.00) [1H, t, J=8.2 (8.4) Hz], 6.87 (7.06) [1H, t, J=8.2 (8.4) Hz], 7.05 (7.24) [1H, d, J=2.8 (2.9) Hz], 7.08 (7.28) [1H, d, J=8.2 (8.4) Hz], 7.52 (7.68) [1H, d, J=8.2 (8.4) Hz], (9.41) 9.45 (1H, brs); ^{13}C NMR ($CDCl_3$–DMSO-d_6) δ 26.7 (26.9), 35.9 (36.2), 54.7 (55.1), 55.3 (55.5), 57.0 (57.3), 80.3 (80.6), 110.4 (110.6), 110.8 (111.1), 111.2 (111.4), 115.1 (115.3), 115.6 (115.9), 117.9 (118.2), 118.5 (118.7), 120.5 (120.8), 121.0 (121.2), 126.4 (126.6), 131.0 (131.1), 135.4 (135.5), 150.7 (150.9), 152.6 (152.8), 166.6 (166.9), 169.4 (169.7) (Signals in brackets belong to the same diastereomer); MS (EI) m/z 425 (M^+), 381, 325, 306, 266, 250, 236; HRMS calcd for $C_{24}H_{27}NO_6$ 425.1838. Found: 428.1839. Anal. Calcd for $C_{24}H_{27}NO_6 \cdot 0.25H_2O$: C, 67.04; H, 6.45; N, 3.26. Found: C, 67.09; H, 6.15; N, 3.20.

(2*S,3*R**)- and (2*S**,3*S**)-2-*tert*-Butoxycarbonyl-3-(5-bromoindol-3-yl)-butyric acid (3g).** From **2g**: 2.93 g (8.0 mmol), pyridine: 10 mL, *tert*-butyl alcohol: 50 mL, reflux: 2 h, chromatography: hexane/acetone 7:3. Yield: 2.30 g (75%); viscous oil; IR (film) 3397, 2966, 1738, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (1.44) (9H, s), 1.47 (3H, d, J=6.6 Hz), 3.67–3.82 (2H, m), 7.02 (1H, brs), 7.15–7.28 (2H, m), 7.78 (1H, s), 8.37 (1H, brs), 9.56 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 19.2 (19.9), (27.3) 27.8, 31.9 (32.1), 58.6 (59.1), (82.5) 82.9, 112.6 (112.6), (112.7) 112.8, (117.1) 117.3, 121.6 (121.9), 122.9 (123.1), 124.8 (124.8), 128.0 (128.1), 134.7 (134.8), 168.4 (168.5), 172.8 (172.9) (Signals in brackets belong to the same diastereomer); MS (EI) m/z 383/381 (M^+), 327/325, 283/281, 222/224. Anal. Calcd for $C_{17}H_{20}BrNO_4$: C, 53.42; H, 5.27; N, 3.66. Found: C, 53.19; H, 5.41; N, 3.62.

General procedure for the preparation of carbamate esters 5a–g

To a suspension of hemiacid esters **3a**–**g** (2.27–7.00 g, 5.94–19.5 mmol) in dry toluene (40–160 mL) were added triethylamine (Et_3N) (0.659–2.36 g, 0.91–3.25 mL, 6.53–23.4 mmol, 1.1–1.2 equiv.) and diphenylphosphoryl azide (DPPA) (2.45–5.92 g, 8.91–21.5 mmol, 1.1–1.5 equiv.). The reaction mixture was heated at 110°C for 2 h under nitrogen atmosphere, then benzyl alcohol (BnOH) (0.706–2.77 g, 0.68–2.65 mL, 6.53–25.6 mmol, 1.1–1.5 equiv.) was added and the heating was continued overnight. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (50 mL), the solution was washed with 5% citric acid, brine and saturated K_2CO_3 solution, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was submitted to flash chromatography (eluent: CH_2Cl_2) to give carbamate esters **5a**–**g**.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-methyltryptophan *tert*-butyl ester (5a).** From **3a**: 3.03 g (10.0 mmol), Et_3N: 1.11 g (11.0 mmol), DPPA: 3.03 g (11.0 mmol), BnOH: 1.30 g (12.0 mmol), toluene: 50 mL. Yield: 3.10 g (76%). The two diastereomers were separated by Chromatotron® (hexane/EtOAc, 1→5% of EtOAc). The analytical samples were crystallized from ether.

(2S,3R*)-**5a**:* mp 114.5–115.5°C (ether); IR (KBr) 3408, 3364, 2979, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.42 (3H, d, J=7.2 Hz), 3.70 (1H, m), 4.59 (1H, dd, J=4.5,

8.6 Hz), 5.10 (2H, s), 5.36 (1H, d, *J*=8.6 Hz), 6.92 (1H, brs), 7.05–7.39 (8H, m), 7.72 (1H, d, *J*=8.1 Hz), 8.27 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 18.0, 27.8, 33.8, 59.2, 66.8, 82.0, 111.1, 116.0, 119.3, 119.4, 121.5, 122.0, 126.6, 128.0, 128.1, 128.5, 136.1, 136.2, 156.2, 170.7; MS (EI) *m/z* 408 (M^+), 335, 307, 261, 244; HRMS calcd for $C_{24}H_{28}N_2O_4$ 408.2049. Found: 408.2030. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.47; H, 6.91; N, 6.88.

(2S,3S*)*-**5a***:* mp 119–120°C (ether); IR (KBr) 3410, 3354, 2976, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (9H, s), 1.40 (3H, d, *J*=7.9 Hz), 3.55 (1H, m), 4.62 (1H, dd, *J*=4.2, 8.5 Hz), 5.05 (2H, m), 5.35 (1H, d, *J*=8.5 Hz), 6.92 (1H, brs), 7.04–7.38 (8H, m), 7.63 (1H, d, *J*=8.1 Hz), 8.19 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 16.9, 27.7, 34.2, 59.2, 66.8, 81.7, 111.2, 116.5, 119.1, 119.3, 121.5, 121.9, 126.7, 127.8, 128.0, 128.4, 136.1, 136.2, 156.0, 170.9; MS (EI) *m/z* 408 (M^+), 335, 307, 261, 244; HRMS calcd for $C_{24}H_{28}N_2O_4$ 408.2049. Found: 408.2038. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.22; H, 6.76; N, 6.79.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-isopropyltryptophan *tert*-butyl ester (5b).** From **3b**: 6.45 g (19.5 mmol), Et_3N: 2.36 g (23.4 mmol), DPPA: 5.90 g (21.45 mmol), BnOH: 2.74 g (25.35 mmol), toluene: 160 mL. Yield: 7.41 g (87%). The two diastereomers were separated by repeated fractional crystallizations (hexane/ether, 3:2).

(2S,3R*)*-**5b**: mp 117–118°C; IR (KBr) 3427, 3352, 2965, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, d, *J*=5.9 Hz), 1.09 (3H, d, *J*=5.9 Hz), 1.19 (9H, s), 2.25 (1H, m), 3.12 (1H, t, *J*=8.6 Hz), 4.78 (1H, t, *J*=8.6 Hz), 5.08 (1H, d, *J*=12.6 Hz), 5.17 (1H, d, *J*=12.6 Hz), 5.19 (1H, d, *J*=8.6 Hz), 6.98 (1H, d, *J*=2.3 Hz), 7.07 (1H, t, *J*=7.7 Hz), 7.18 (1H, t, *J*=7.7 Hz), 7.29–7.39 (6H, m), 7.55 (1H, d, *J*=7.7 Hz), 8.11 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 20.0, 21.7, 27.6, 29.6, 46.7, 56.9, 66.8, 81.5, 110.9, 112.8, 119.4, 119.5, 121.9, 122.5, 128.1, 128.5, 128.8, 128.9, 135.6, 136.4, 155.7, 170.8; MS (EI) *m/z* 436 (M^+), 173, 172, 157, 130; HRMS calcd for $C_{26}H_{32}N_2O_4$ 436.2362. Found: 436.2362. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.41. Found: C, 71.38; H, 7.62; N, 6.38.

(2S,3S*)*-**5b***:* mp 132–133°C; IR (KBr) 3427, 3352, 2976, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (3H, d, *J*=5.9 Hz), 1.19 (3H, d, *J*=5.9 Hz), 1.28 (9H, s), 2.17 (1H, m), 3.23 (1H, dd, *J*=4.1, 9.0 Hz), 4.82 (1H, dd, *J*=4.1, 9.5 Hz), 5.09 (1H, d, *J*=13.5 Hz), 5.15 (1H, d, *J*=13.5 Hz), 5.20 (1H, d, *J*=9.5 Hz), 6.99 (1H, d, *J*=1.4 Hz), 7.09 (1H, t, *J*=7.7 Hz), 7.18 (1H, t, *J*=7.7 Hz), 7.29–7.40 (6H, m), 7.62 (1H, d, *J*=7.7 Hz), 8.09 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.7, 27.8, 29.6, 46.6, 56.5, 66.8, 81.9, 111.1, 113.5, 119.4, 119.8, 122.0, 122.1, 127.9, 128.0, 128.4, 128.5, 136.0, 136.4, 156.5, 171.3; MS (EI) *m/z* 436 (M^+), 173, 172, 157, 130; HRMS calcd for $C_{26}H_{32}N_2O_4$ 436.2362. Found: 436.2359. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.41. Found: C, 71.44; H, 7.57; N, 6.71.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-(3-pentyl)-tryptophan *tert*-butyl ester (5c).** From **3c**: 7.00 g (19.5 mmol), Et_3N: 2.36 g (23.4 mmol), DPPA: 5.90 g (21.45 mmol), BnOH: 2.74 g (25.35 mmol), toluene: 160 mL. Yield: 7.82 g (86%); viscous oil; IR (film) 3412, 3352, 2965, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68–0.80 (3H, m), 0.91–1.02 (3H, m), 1.15 (1.29) (9H, s), 1.40–1.59 (4H, m), 1.80 (1H, m), 3.37 (3.53) [1H, t, *J*=6.8 Hz (dd, *J*=4.1, 9.5 Hz)], 4.68–4.83 (1H, m), 5.03–5.23 (3H, m), (6.91) 6.94 [1H, (brs) d, *J*=1.8 Hz], 7.06–7.39 (8H, m), 7.54 (7.61) (1H, d, *J*=7.7 Hz), 8.29 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 9.4 (11.3), 10.4 (10.8), 21.3 (22.3), 22.0 (22.7), (27.6) 27.8, (40.8) 41.6, 41.3 (41.9), 56.2 (56.7), 66.8 (66.8), (81.5) 81.8, (110.9) 111.1, (112.7) 113.1, 119.2 (119.6), (119.3) 119.7, (121.7) 121.9, 122.3 (122.7), (126.9) 127.9, 127.6 (128.1), 128.0 (128.4), 128.7 (128.8), (135.5) 136.0, 136.4 (136.4), (155.7) 156.5, (171.5) 172.9 (Signals in brackets belong to the same diastereomer); MS (EI) *m/z* 464 (M^+), 200, 130; HRMS calcd for $C_{28}H_{36}N_2O_4$ 464.2675. Found: 464.2675. Anal. Calcd for $C_{28}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.15; H, 7.99; N, 6.11.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-cyclohexyltryptophan *tert*-butyl ester (5d).** From **3d**: 5.42 g (14.6 mmol), Et_3N:1.77 g (17.52 mmol), DPPA: 4.42 g (16.06 mmol), BnOH: 2.36 g (21.9 mmol), toluene: 70 mL. Yield: 6.07 g (87%); viscous oil; IR (film) 3412, 3358, 2986, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70–1.18 (5H, m), 1.22 (1.28) (9H, s), 1.47–1.90 (5H, m), 2.05 (2.20) (1H, m), 3.15 (3.30) [1H, t, *J*=7.0 Hz (dd, *J*=4.4, 9.1 Hz)], 4.75–4.92 (1H, m), 5.01–5.28 (3H, m), 6.93 (1H, brs), 7.04–7.40 (8H, m), 7.54 (7.60) (1H, d, *J*=7.8 Hz), (8.12) 8.17 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 26.1 (26.4), (27.7) 27.9, (30.3) 30.6, 31.7 (32.0), 39.1 (39.6), 45.4 (45.6), (55.7) 56.1, 66.8 (66.8), (81.5) 81.8, 110.9 (111.3), (113.1) 113.4, 119.4 (119.7), (119.6) 119.9, (121.9) 122.3, (122.0) 122.1, 127.8 (127.8), 127.9 (127.9), 128.1 (128.1), 128.5 (128.5), (135.6) 136.2, (135.7) 136.0, (155.9) 156.4, (172.1) 172.9 (Signals in brackets belong to the same diastereomer); MS (EI) *m/z* 476 (M^+), 401, 360, 212, 181, 130. Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 72.85; H, 7.50; N, 5.85.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-phenyltryptophan *tert*-butyl ester (5e).** From **3e**: 3.65 g (10.0 mmol), Et_3N: 1.11 g (11.0 mmol), DPPA: 3.03 g (11.0 mmol), BnOH: 1.30 g (12.0 mmol), toluene: 50 mL. Yield: 4.37 g (93%); viscous oil; IR (film) 3414, 3347, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.15 (1.21) (9H, s), 4.67 (4.75) [1H, d, *J*=9.1 (8.1) Hz], 4.91–5.12 (3H, m), (5.73) 5.97 (1H, d, *J*=9.0 Hz), 6.92–7.45 (15H, m), 9.72 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 27.3 (27.4), 44.6 (45.2), 58.7 (58.9), 65.5 (65.6), 80.2 (80.4), 111.5 (111.6), 114.4 (115.0), (118.5) 118.6, (118.8) 118.9, (121.2) 121.7, (126.4) 126.5, 126.6 (126.9), (127.2) 127.3, 127.6 (127.7), (127.7) 127.8, (127.9) 127.95, 128.0 (128.1), (128.3) 128.5, (129.1) 130.3, (136.4) 137.2, (141.5) 142.8, 156.0 (156.3), (170.9) 171.1 (Signals in brackets belong to the same diastereomer); MS (EI) *m/z* 470 (M^+), 370, 340, 279, 234, 208; HRMS calcd for $C_{29}H_{30}N_2O_4$ 470.2206. Found: 470.2204. Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 73.85; H, 6.45; N, 5.86.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-(2,5-dimethoxyphenyl)-tryptophan *tert*-butyl ester (5f).** From

3f: 4.25 g (10.0 mmol), Et_3N: 1.11 g (11.0 mmol), DPPA: 3.03 g (11.0 mmol), BnOH: 1.30 g (12.0 mmol), toluene: 50 mL. Yield: 4.76 g (90%); viscous oil; IR (film) 3414, 3367, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (1.18) (9H, s), 3.61 (3.64) (3H, s), 3.82 (3.85) (3H, s), 4.93–5.20 (4H, m), (5.43) 5.58 (1H, d, J=9.1 Hz), 6.62–6.83 (3H, m), 6.96–7.52 (10H, m), (8.47) 8.52 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.4 (27.5), 38.1 (39.2), 55.4 (55.6), 55.7 (56.0), (57.5) 57.9, 66.6 (66.6), 81.3 (81.5), (111.0) 111.4, 111.6 (111.6), 112.0 (112.2), 114.1 (114.2), 116.1 (116.5), 118.9 (118.9), 119.2 (119.3), (121.9) 122.2, 122.9 (123.3), 127.3 (127.4), 127.7 (127.7), 127.8 (127.9), 128.3 (128.3), 129.8 (129.8), (135.9) 136.0, 136.4 (136.4), (151.4) 152.6, (153.3) 153.5, 155.8 (156.0), (170.9) 171.2 (Signals in brackets belong to the same diastereomer); MS (EI) m/z 530 (M^+), 485, 458, 430, 267. Anal. Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 70.29; H, 6.66; N, 5.30.

(2*S,3*R**)- and (2*S**,3*S**)-α-*N*-Benzyloxycarbonyl-β-methyl-5-bromotryptophan *tert*-butyl ester (5g).** From **3g**: 2.27 g (5.94 mmol), Et_3N: 0.66 g (6.53 mmol), DPPA: 2.45 g (8.91 mmol), BnOH: 7.06 g (6.53 mmol), toluene: 40 mL. Yield: 2.33 g (81%). The two diastereomers were separated by Chromatotron® (hexane/methyl *tert*-butyl ether, 9:1).

(2S,3R*)*-**5g**: viscous oil; IR (film) 3416, 3360, 2974, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (9H, s), 1.42 (3H, d, J=7.2 Hz), 3.70 (1H, m), 4.58 (1H, dd, J=4.6, 8.8 Hz), 5.13 (2H, s), 5.32 (1H, d, J=8.8 Hz), 6.99 (1H, d, J=1.9 Hz), 7.13–7.42 (7H, m), 7.85 (1H, s), 8.35 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 18.4, 27.9, 33.6, 59.1, 67.0, 82.4, 112.6, 112.7, 115.9, 122.0, 122.7, 125.0, 128.1, 128.2, 128.3, 128.5, 134.6, 136.2, 156.3, 170.6; MS (EI) m/z 488/486 (M^+), 415/413, 387/385, 341/339, 324/322. Anal. Calcd for $C_{24}H_{27}BrN_2O_4$: C, 59.15; H, 5.58; N, 5.75. Found: C, 59.06; H, 5.55; N, 5.79.

(2S,3S*)*-**5g**: viscous oil; IR (film) 3418, 3358, 3061, 2966 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.37 (3H, d, J=7.0 Hz), 3.49 (1H, m), 4.57 (1H, dd, J=6.0, 9.0 Hz), 5.06 (2H, s), 5.36 (1H, d, J=9.0 Hz), 6.94 (1H, d, J=2.1 Hz), 7.12–7.40 (7H, m), 7.76 (1H, s), 8.24 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 16.7, 27.8, 34.2, 59.2, 66.9, 82.0, 112.6, 112.7, 116.5, 121.7, 122.8, 124.8, 127.0, 128.1, 128.4, 128.5, 134.7, 136.3, 156.0, 170.7; MS (EI) m/z 488/486 (M^+), 415/413, 387/385, 341/339, 324/322. Anal. Calcd for $C_{24}H_{27}BrN_2O_4$: C, 59.15; H, 5.58; N, 5.75. Found: C, 59.25; H, 5.55; N, 5.70.

General procedure for the preparation of amino esters 6a–f by the debenzylation of carbamate esters 5a–f

A solution of carbamate esters **5a**–**f** (2.45–7.80 g, 6.00–16.8 mmol) in a mixture of ethanol (70–120 mL), acetic acid (0.570–1.21 g, 0.54–1.15 mL, 9.50–20.2 mmol), and, when necessary, ethyl acetate (70 mL) as co-solvent was hydrogenated over 10% Pd/C (0.368–1.95 g). After hydrogen consumption had ceased, the catalyst was filtered off over celite, and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, the pH was rendered alkaline (pH=9) by 10% Na_2CO_3 solution, and the organic phase was either purified by Chromatotron® or directly crystallized to give aminoesters **6a**–**f**.

(2S*,3R*)- and (2S*,3S*)-β-Methyltryptophan *tert*-butyl ester (6a). From **5a**: 2.45 g (6.00 mmol), EtOH: 70 mL, AcOH: 0.54 mL, Pd/C catalyst: 0.368 g, crystallization: ether.

(2S,3R*)*-**6a**: yield: 1.49 g (91%); mp 94–96°C; IR (KBr) 3408, 3364, 2980, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 1.42 (3H, d, J=7.7 Hz), 1.67 (2H, brs), 3.40 (1H, dq, J=7.7 Hz), 3.61 (1H, d, J=7.7 Hz), 6.96 (1H, d, J=2.6 Hz), 7.04–7.18 (2H, m), 7.28 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=8.2 Hz), 8.67 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 18.9, 27.9, 36.4, 60.6, 81.1, 111.3, 116.8, 119.0, 119.3, 121.7, 121.8, 126.8, 136.3, 174.3; MS (EI) m/z 274 (M^+), 255, 173, 158, 144; HRMS calcd for $C_{16}H_{22}N_2O_2$ 274.1681. Found: 274.1679. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.01; H, 8.08; N, 10.21. Found: C, 70.12; H, 7.98; N, 10.24.

(2S,3S*)*-**6a**: yield: 1.54 g (94%); mp 97–98.5°C; IR (KBr) 3408, 3360, 2979, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, d, J=7.3 Hz), 1.46 (9H, s), 1.78 (2H, brs), 3.61 (1H, m), 3.81 (1H, d, J=4.5 Hz), 6.95 (1H, d, J=2.5 Hz), 7.06–7.20 (2H, m), 7.30 (1H, d, J=8.9 Hz), 7.65 (1H, d, J=8.6 Hz), 8.60 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 13.6, 27.9, 34.6, 58.6, 80.9, 111.3, 117.7, 118.8, 119.1, 121.7, 121.9, 126.4, 136.4, 173.9; MS (EI) m/z 274 (M^+), 255, 173, 158, 144; HRMS calcd for $C_{16}H_{22}N_2O_2$ 274.1681. Found: 274.1685. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.01; H, 8.08; N, 10.21. Found: C, 70.29; H, 8.26; N, 10.18.

(2S*,3R*)- and (2S*,3S*)-β-Isopropyltryptophan *tert*-butyl ester (6b). From **5b**: 7.33 g (16.8 mmol), EtOH: 120 mL, AcOH: 1.15 mL, Pd/C catalyst: 1.83 g, crystallization: hexane/ether 10:1.

(2S,3R*)*-**6b**: yield: 4.88 g (96%); mp 141–143°C; IR (KBr) 3364, 3302, 2959, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, J=5.9 Hz), 0.99 (3H, d, J=5.9 Hz), 1.15 (9H, s), 1.61 (2H, brs), 2.41 (1H, m), 3.12 (1H, t, J=8.1 Hz), 3.74 (1H, d, J=8.1 Hz), 6.94 (1H, d, J=0.9 Hz), 7.09 (1H, t, J=7.7 Hz), 7.16 (1H, t, J=7.7 Hz), 7.32 (1H, d, J=7.7 Hz), 7.63 (1H, d, J=7.7 Hz), 8.39 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 19.1, 21.8, 27.8, 28.6, 47.0, 58.4, 80.5, 110.8, 114.0, 119.1, 119.5, 121.6, 122.4, 128.9, 135.6, 174.8; MS (EI) m/z 302 (M^+), 201, 172, 158, 130; HRMS calcd for $C_{18}H_{26}N_2O_2$ 302.1994. Found: 302.1992. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.62; H, 8.86; N, 9.37.

(2S,3S*)*-**6b**: yield: 3.87 g (76%); mp 125–127°C; IR (KBr) 3381, 3171, 2974, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (3H, d, J=5.9 Hz), 1.08 (3H, d, J=5.9 Hz), 1.25 (9H, s), 1.67 (2H, brs), 2.19 (1H, m), 3.15 (1H, dd, J=5.0, 9.0 Hz), 3.88 (1H, d, J=5.0 Hz), 7.07 (1H, d, J=2.3 Hz), 7.09 (1H, t, J=7.7 Hz), 7.17 (1H, t, J=7.7 Hz), 7.31 (1H, d, J=7.7 Hz), 7.67 (1H, d, J=7.7 Hz), 8.42 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.6, 27.8, 30.7, 47.2, 56.8, 81.0, 110.9, 114.1, 119.0, 119.7, 121.7, 121.9, 128.6, 135.8, 174.8; MS (EI) m/z 302 (M^+), 201, 172, 158, 130; HRMS calcd for $C_{18}H_{26}N_2O_2$ 302.1994. Found: 302.1988. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.71; H, 8.83; N, 9.46.

(2S*,3R*)- and (2S*,3S*)-β-(3-Pentyl)-tryptophan *tert*-butyl ester (6c). From **5c**: 7.80 g (16.8 mmol), EtOH:

120 mL, AcOH: 1.15 mL, Pd/C catalyst: 1.95 g. Yield: 3.90 g (70%). The two diastereomers were separated by Chromatotron® (CH_2Cl_2). The analytical samples were crystallized from ether.

(2S,3R*)*-**6c**: mp 159–160°C; IR (KBr) 3370, 2965, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J=6.8 Hz), 1.00 (3H, t, J=6.8 Hz), 1.12 (9H, s), 1.22–1.68 (6H, m), 1.93 (1H, m), 3.31 (1H, t, J=7.7 Hz), 3.75 (1H, d, J=7.7 Hz), 6.99 (1H, d, J=1.8 Hz), 7.05–7.20 (2H, m), 7.32 (1H, d, J=7.7 Hz), 7.64 (1H, d, J=7.7 Hz), 8.09 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 11.5, 11.6, 22.7, 23.0, 27.5, 41.7, 42.7, 58.2, 80.4, 110.8, 114.1, 119.1, 119.5, 121.5, 122.5, 128.9, 135.5, 174.9; MS (EI) *m/z* 330 (M^+), 200, 130. Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.49; H, 8.92; N, 8.30.

(2S,3S*)*-**6c**: mp 111–113°C; IR (KBr) 3377, 3171, 2967, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (3H, t, J=6.8 Hz), 0.98 (3H, t, J=6.8 Hz), 1.28 (9H, s), 1.30–1.58 (6H, m), 1.82 (1H, m), 3.43 (1H, dd, J=5.0, 9.0 Hz), 3.85 (1H, d, J=5.0 Hz), 6.99 (1H, d, J=1.8 Hz), 7.06–7.19 (2H, m), 7.30 (1H, d, J=7.7 Hz), 7.67 (1H, d, J=7.7 Hz), 8.39 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 9.9, 11.2, 21.9, 22.4, 27.6, 42.1, 42.2, 56.6, 80.9, 111.0, 114.0, 119.0, 119.7, 121.7, 122.1, 128.7, 135.8, 174.9; MS (EI) *m/z* 330 (M^+), 200, 130; HRMS calcd for $C_{20}H_{30}N_2O_2$ 330.2312. Found: 330.2307. Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.72; H, 9.23; N, 8.57.

(2S*,3R*)- and (2S*,3S*)-β-Cyclohexyltryptophan *tert*-butyl ester (6d). From **5d**: 6.81 g (14.3 mmol), EtOH: 105 mL, AcOH: 0.98 mL, Pd/C catalyst: 1.75 g, crystallization: ether. Yield: 3.20 g (65%); mp 220–222°C (dec); IR (KBr) 3362, 3190, 2977, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.40 (5H, m), 1.18 (1.26) (9H, s), 1.49–1.94 (7H, m), (2.00) 2.03 (1H, m), 3.12 (3.18) [1H, t, J=8.2 Hz (dd, J=5.0, 8.7 Hz)], 3.77 (3.90) [1H, d, J=8.2 (5.0) Hz], 6.97 (1H, d, J=1.9 Hz), 7.03–7.21 (2H, m), 7.33 (1H, d, J=7.8 Hz), 7.63 (1H, d, J=7.9 Hz), 8.12 (8.32) (1H, brs); ^{13}C NMR ($CDCl_3$) δ 26.3 (26.4), 27.5 (27.8), 29.7 (30.8), (31.8) 32.0, 38.9 (40.2), (46.1) 46.5, (55.9) 56.9, 80.7 (81.0), 110.9 (111.0), 113.5 (114.2), 118.8 (119.0), 119.1 (119.7), 121.3 (121.7), (121.9) 122.3, 128.7 (128.7), 135.6 (135.7), 174.5 (174.9) (Signals in brackets belong to the same diastereomer); MS (EI) *m/z* 342 (M^+), 241, 212, 158, 130. Anal. Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18. Found: C, 73.34; H, 9.11; N, 8.16.

(2S*,3R*)- and (2S*,3S*)-β-Phenyltryptophan *tert*-butyl ester (6e). From **5e**: 2.82 g (6.00 mmol), EtOH: 70 mL, AcOH: 0.54 mL, EtOAc: 70 mL, Pd/C catalyst: 0.423 g. Yield: 1.49 g (74%). The two diastereomers were separated by Chromatotron® (CH_2Cl_2/MeOH/concd NH_4OH, 98.5:1:0.5). The analytical samples were crystallized from ether.

(2S,3R*)*-**6e**: mp 175–176°C; IR (KBr) 3410, 3057, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (9H, s), 1.56 (2H, brs), 4.17 (1H, d, J=7.2 Hz), 4.60 (1H, d, J=7.2 Hz), 7.04 (1H, t, J=7.8 Hz), 7.11 (1H, t, J=7.8 Hz), 7.23–7.40 (7H, m), 7.46 (1H, d, J=7.8 Hz), 8.52 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.6, 47.3, 59.4, 81.1, 111.0, 116.1, 119.1, 119.2, 121.8, 122.4, 126.7, 126.8, 128.3, 128.8, 136.1, 140.6, 173.6; MS (EI) *m/z* 336 (M^+), 278, 235, 207; HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838. Found: 336.1836. Anal. Calcd for $C_{21}H_{24}N_2O_2 \cdot 0.5H_2O$: C, 73.02; H, 7.30; N, 8.11. Found: C, 73.14; H, 7.05; N, 8.20.

(2S,3S*)*-**6e**: mp 150–152°C; IR (KBr) 3410, 3059, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (9H, s), 1.67 (2H, brs), 4.14 (1H, d, J=8.6 Hz), 4.59 (1H, d, J=8.6 Hz), 7.04 (1H, t, J=8.3 Hz), 7.11–7.42 (7H, m), 7.51 (1H, d, J=8.3 Hz), 8.21 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.3, 48.5, 59.6, 81.2, 111.2, 114.3, 118.6, 119.0, 121.6, 121.8, 126.3, 127.1, 128.0, 128.3, 136.2, 141.4, 173.1; MS *m/z* 336 (M^+), 261, 235, 206; HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838. Found: 336.1836. Anal. Calcd for $C_{21}H_{24}N_2O_2 \cdot 0.5H_2O$: C, 73.02; H, 7.30; N, 8.11. Found: C, 72.70; H, 7.01; N, 7.87.

(2S*,3R*)- and (2S*,3S*)-β-(2,5-Dimethoxyphenyl)-tryptophan *tert*-butyl ester (6f). From **5f**: 3.18 g (6.00 mmol), EtOH: 70 mL, AcOH: 0.54 mL, EtOAc: 70 mL, Pd/C catalyst: 0.477 g. Yield: 2.02 g (85%). The two diastereomers were separated by Chromatotron® (CH_2Cl_2/MeOH/concd NH_4OH, 98.5:1:0.5). The analytical sample of (2S*,3R*)-**6f** was crystallized from ether.

(2S,3R*)*-**6f**: mp 104–105°C; IR (KBr) 3401, 3375, 2978, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (9H, s), 1.71 (2H, brs), 3.66 (3H, s), 3.82 (3H, s), 4.26 (1H, d, J=7.4 Hz), 5.04 (1H, d, J=7.4 Hz), 6.67 (1H, dd, J=2.8, 7.9 Hz), 6.77 (1H, d, J=7.9 Hz), 6.91 (1H, d, J=2.1 Hz), 7.03 (1H, t, J=7.8 Hz), 7.12 (1H, t, J=7.8 Hz), 7.24 (1H, d, J=2.8 Hz), 7.26 (1H, d, J=7.8 Hz), 7.59 (1H, d, J=7.8 Hz), 8.67 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.5, 41.1, 55.5, 56.0, 58.2, 80.7, 111.0, 111.3, 111.4, 114.9, 116.8, 118.9, 119.1, 121.7, 122.4, 127.8, 131.3, 135.8, 151.2, 153.3, 173.6; MS (EI) *m/z* 396 (M^+), 365, 341, 295, 266, 130. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.06. Found: C, 70.01; H, 7.35; N, 7.10.

(2S,3S*)*-**6f**: viscous oil; IR (film) 3377, 2976, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (9H, s), 1.77 (2H, brs), 3.65 (3H, s), 3.79 (3H, s), 4.14 (1H, d, J=8.6 Hz), 5.06 (1H, d, J=8.6 Hz), 6.67 (1H, dd, J=2.4, 8.1 Hz), 6.78 (1H, d, J=8.1 Hz), 6.96 (1H, d, J=2.1 Hz), 7.02 (1H, t, J=7.9 Hz), 7.10 (1H, t, J=7.9 Hz), 7.17 (1H, d, J=2.4 Hz), 7.25 (1H, d, J=7.9 Hz), 7.58 (1H, d, J=7.9 Hz), 8.53 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 27.5, 39.9, 55.4, 56.0, 59.3, 80.6, 110.9, 111.3, 111.5, 115.6, 115.7, 119.0, 119.1, 121.7, 122.4, 127.2, 131.1, 135.8, 151.8, 153.4, 173.9; MS (EI) *m/z* 396 (M^+), 365, 341, 295, 266, 130. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.06. Found: C, 69.82; H, 7.01; N, 7.10.

General procedure for the preparation of tryptophans 7a–e,g from carbamate esters 5a,b,d,g and amino esters 6c,e

The appropriate carbamate ester **5** or amino ester **6** (150–330 mg, 0.31–0.89 mmol) was dissolved in CH_2Cl_2 (5 mL), cooled to −10°C, and 1 M BBr_3 in CH_2Cl_2 (1.55–4.45 mL, 1.55–4.45 mmol, 5.0 equiv.) was added dropwise with stirring. The stirring was continued at −10°C for 1 h and at

room temperature for 5 h. The excess of BBr_3 was destroyed by the careful addition of water (10–25 mL). The layers were separated, the organic phase was washed with water, and the combined aqueous layers were evaporated to dryness. MeOH was evaporated several times from the residue. Crude tryptophans **7a**–**e**,**g** were purified on preparative TLC plates (BuOH/MeOH/concd NH_4OH, 5:4:1) and then solidified with hexane/ether.

(2*S,3*R**)- and (2*S**,3*S**)-β-Methyltryptophan (7a).** From **5a**: 300 mg (0.74 mmol), 1 M BBr_3 in CH_2Cl_2: 3.70 mL (5.0 equiv.).

(2S,3R*)*-**7a**: yield: 188 mg (85%); amorphous powder; IR (KBr) 3420, 2905, 1736 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.46 (3H, d, *J*=7.2 Hz), 3.72 (1H, m), 4.10 (1H, brs), 6.90–7.14 (2H, m), 7.27 (1H, d, *J*=2.0 Hz), 7.40 (1H, d, *J*=8.0 Hz), 7.64 (1H, d, *J*=8.0 Hz), 8.29 (3H, brs), 11.13 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 17.2, 31.9, 57.0, 111.7, 113.0, 118.7, 118.8, 121.3, 123.9, 126.3, 136.4, 170.2; MS (ESI) *m/z* 219 (M^++1 for the free amino acid). Anal. Calcd for $C_{12}H_{14}N_2O_2HBr{\cdot}0.5H_2O$: C, 46.77; H, 5.23; N, 9.09. Found: C, 47.11; H, 5.44; N, 9.32.

(2S,3S*)*-**7a**: yield: 202 mg (91%); amorphous powder; IR (KBr) 3418, 2914, 1736 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (3H, d, *J*=7.1 Hz), 3.39 (1H, m), 4.12 (1H, brs), 7.02 (1H, t, *J*=7.5 Hz), 7.11 (1H, t, *J*=7.5 Hz), 7.25 (1H, d, *J*=3.0 Hz), 7.41 (1H, d, *J*=7.5 Hz), 7.58 (1H, d, *J*=7.5 Hz), 8.17 (3H, brs), 11.16 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 16.0, 31.9, 57.0, 111.9, 112.8, 118.4, 118.8, 121.4, 124.0, 126.1, 136.6, 170.5; MS (ESI) *m/z* 219 (M^++1 for the free amino acid). Anal. Calcd for $C_{12}H_{14}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 45.44; H, 5.40; N, 8.83. Found: C, 45.70; H, 5.69; N, 8.80.

(2*S,3*R**)- and (2*S**,3*S**)-β-Isopropyltryptophan (7b).** From **5b**: 330 mg (0.76 mmol), 1 M BBr_3 in CH_2Cl_2: 3.80 mL (5.0 equiv.).

(2S,3R*)*-**7b**: yield 217 mg (87%); amorphous powder; IR (KBr) 3405, 3352, 2963, 1728 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.70 (3H, d, *J*=5.9 Hz), 1.11 (3H, d, *J*=5.9 Hz), 2.49 (1H, m), 3.28 (1H, dd, *J*=5.0, 8.1 Hz), 4.19 (1H, d, *J*=5.0 Hz), 6.98 (1H, t, *J*=7.7 Hz), 7.09 (1H, t, *J*=7.7 Hz), 7.19 (1H, brs), 7.38 (1H, d, *J*=7.7 Hz), 7.58 (1H, d, *J*=7.7 Hz), 8.36 (3H, brs), 11.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 20.8, 21.7, 32.1, 45.4, 54.2, 109.5, 111.6, 118.6, 119.2, 121.0, 124.9, 127.7, 136.3, 170.5; MS (ESI) *m/z* 247 (M^++1 for the free amino acid). Anal. Calcd for $C_{14}H_{18}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 48.71; H, 6.13; N, 8.11. Found: C, 48.53; H, 6.00; N, 8.02.

(2S,3S*)*-**7b**: yield 162 mg (65%); amorphous powder; IR (KBr) 3362, 3258, 2965, 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.82 (3H, d, *J*=6.2 Hz), 1.02 (3H, d, *J*=6.2 Hz), 2.28 (1H, m), 3.39 (1H, dd, *J*=5.0, 8.6 Hz), 4.24 (1H, d, *J*=5.0 Hz), 7.01 (1H, t, *J*=7.8 Hz), 7.10 (1H, t, *J*=7.8 Hz), 7.29 (1H, d, *J*=3.6 Hz), 7.40 (1H, d, *J*=7.8 Hz), 7.55 (1H, d, *J*=7.8 Hz), 8.20 (3H, brs), 11.08 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 20.3, 21.6, 29.3, 43.9, 54.6, 109.0, 111.5, 118.7, 118.8, 121.2, 124.2, 128.1, 136.1, 171.0; MS (ESI) *m/z* 247 (M^++1 for the free amino acid). Anal. Calcd for $C_{14}H_{18}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 48.71; H, 6.13; N, 8.11. Found: C, 48.36; H, 6.40; N, 8.29.

(2*S,3*R**)- and (2*S**,3*S**)-β-(3-Pentyl)-tryptophan (7c).** From **6c**: 200 mg (0.61 mmol), 1 M BBr_3 in CH_2Cl_2: 3.05 mL (5.0 equiv.).

(2S,3R*)*-**7c**: yield 169 mg (78%); amorphous powder; IR (KBr) 3455, 2928, 1707 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.93 (3H, t, *J*=7.2 Hz), 0.99 (3H, t, *J*=7.3 Hz), 1.05–1.66 (4H, m), 1.95 (1H, m), 3.69 (1H, brs), 4.13 (1H, d, *J*=2.3 Hz), 7.20 (1H, t, *J*=7.5 Hz), 7.29 (1H, d, *J*=2.0 Hz), 7.43 (1H, t, *J*=7.5 Hz), 7.54 (1H, d, *J*=7.5 Hz), 7.74 (1H, d, *J*=7.5 Hz), 8.69 (3H, brs), 12.09 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 12.6, 12.8, 24.0, 24.4, 42.7, 43.2, 60.6, 111.7, 114.3, 121.1, 122.5, 122.6, 127.9, 136.5, 144.7, 170.4; MS (ESI) *m/z* 275 (M^++1 for the free amino acid). Anal. Calcd for $C_{16}H_{22}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 51.48; H, 6.75; N, 7.50. Found: C, 51.20; H, 6.59; N, 7.58.

(2S,3S*)*-**7c**: yield: 195 mg (90%); amorphous powder; IR (KBr) 3432, 2930, 1703 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.91 (3H, t, *J*=7.1 Hz), 0.99 (3H, t, *J*=7.3 Hz), 1.07–1.70 (4H, m), 2.22 (1H, m), 3.45 (1H, dd, *J*=4.8, 9.8 Hz), 4.19 (1H, d, *J*=4.8 Hz), 6.98 (1H, t, *J*=7.8 Hz), 7.07 (1H, t, *J*=7.8 Hz), 7.15 (1H, d, *J*=2.0 Hz), 7.38 (1H, d, *J*=7.8 Hz), 7.57 (1H, d, *J*=7.8 Hz), 8.16 (3H, brs), 11.16 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 9.6, 10.4, 21.2, 21.8, 40.8, 40.9, 54.3, 111.6, 114.3, 118.8, 121.2, 127.9, 128.0, 136.6, 144.7, 171.1; MS (ESI) *m/z* 275 (M^++1 for the free amino acid). Anal. Calcd for $C_{16}H_{22}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 51.48; H, 6.75; N, 7.50. Found: C, 51.85; H, 7.09; N, 7.61.

(2*S,3*R**)- and (2*S**,3*S**)-β-Cyclohexyltryptophan (7d).** From **5d**: 300 mg (0.63 mmol), 1 M BBr_3 in CH_2Cl_2: 3.15 mL (5.0 equiv.). Yield: 188 mg (81%); amorphous powder; IR (KBr) 3472, 3422, 2924, 1728 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.65–1.80 (10H, m), 1.90 (2.10) (1H, m), (3.30) 3.43 (1H, brs), 4.25 (1H, m), 6.90–7.85 (5H, m), (8.21) 8.67 (3H, brs), (11.15) 12.07 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 25.7 (25.9), 26.2 (26.3), 29.8 (30.4), (37.8) 38.6, 44.3 (44.3), (53.8) 54.2, 109.2 (109.3), 111.6 (111.7), 114.3 (119.1), 118.6 (118.7), (121.1) 121.2, 124.1 (124.9), 136.0 (136.2), 144.7 (144.9), (170.6) 171.1 (Signals in brackets belong to the same diastereomer); MS (ESI) *m/z* 287 (M^++1 for the free amino acid). Anal. Calcd for $C_{17}H_{22}N_2O_2{\cdot}HBr{\cdot}0.5H_2O$: C, 54.26; H, 6.43; N, 7.44. Found: C, 54.55; H, 6.12; N, 7.81.

(2*S,3*R**)- and (2*S**,3*S**)-β-Phenyltryptophan (7e).** From **6e**: 300 mg (0.89 mmol), 1 M BBr_3 in CH_2Cl_2: 4.45 mL (5.0 equiv.).

(2S,3R*)*-**7e**: yield: 296 mg (92%); amorphous powder; IR (KBr) 3418, 2888, 1738 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.71 (1H, m), 4.78 (1H, d, *J*=9.0 Hz), 6.95 (1H, t, *J*=7.4 Hz), 7.06 (1H, t, *J*=7.4 Hz), 7.18–7.48 (7H, m), 7.53 (1H, d, *J*=7.4 Hz), 8.42 (3H, brs), 11.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 43.9, 56.4, 111.7, 112.0, 118.4, 118.8, 121.4, 123.8, 126.5, 127.3, 128.8, 128.9, 136.0, 139.6, 170.3; MS (ESI) *m/z* 281 (M^++1 for the free amino acid). Anal. Calcd for $C_{17}H_{16}N_2O_2{\cdot}HBr{\cdot}H_2O$: C, 53.84; H, 5.05; N, 7.38. Found: C, 53.46; H, 4.71; N, 7.21.

(2S,3S*)*-**7e**: yield: 266 mg (83%); amorphous powder; IR (KBr) 3252, 2882, 2778, 1676 cm^{-1}; ^1H NMR (DMSO-d_6)

δ 4.65 (1H, d, *J*=8.3 Hz), 4.73 (1H, m), 6.98 (1H, t, *J*=7.6 Hz), 7.07 (1H, t, *J*=7.6 Hz), 7.11–7.53 (7H, m), 7.77 (1H, d, *J*=1.5 Hz), 8.45 (3H, brs), 11.30 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 44.6, 56.4, 111.7, 112.2, 118.4, 118.8, 121.5, 123.5, 126.7, 127.2, 128.5, 128.7, 136.4, 140.0, 170.2; MS (ESI) *m/z* 281 (M^++1 for the free amino acid). Anal. Calcd for $C_{17}H_{16}N_2O_2$·HBr·0.5H_2O: C, 55.15; H, 4.90; N, 7.56. Found: C, 55.50; H, 4.66; N, 7.42.

(2*S,3*R**)- and (2*S**,3*S**)-β-Methyl-5-bromotryptophan (7g).** From **5g**: 150 mg (0.31 mmol), 1 M BBr_3 in CH_2Cl_2: 1.55 mL (5.0 equiv.).

(2S,3R*)*-**7g**: yield: 96 mg (82%); amorphous powder; IR (KBr) 3383, 2928, 1732 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.43 (3H, d, *J*=7.2 Hz), 3.67 (1H, m), 4.08 (1H, d, *J*=4.9 Hz), 7.19 (1H, dd, *J*=1.9, 8.6 Hz), 7.34 (1H, d, *J*=3.6 Hz), 7.37 (1H, d, *J*=8.6 Hz), 7.96 (1H, d, *J*=1.9 Hz), 8.31 (3H, brs), 11.37 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 16.9, 31.0, 57.1, 111.5, 113.1, 113.8, 121.0, 123.8, 125.6, 128.2, 135.1, 170.2; MS (ESI) *m/z* 289/287 (M^++1 for the free amino acid). Anal. Calcd for $C_{12}H_{13}BrN_2O_2$·HBr·H_2O: C, 36.39; H, 4.07; N, 7.07. Found: C, 36.76; H, 4.29; N, 6.94.

(2S,3S*)*-**7g**: yield: 89 mg (76%); amorphous powder; IR (KBr) 3412, 2969, 1740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.43 (3H, d, *J*=7.2 Hz), 3.70 (1H, m), 4.12 (1H, brs), 7.21 (1H, dd, *J*=1.7, 8.6 Hz), 7.29 (1H, d, *J*=2.5 Hz), 7.39 (1H, d, *J*=8.6 Hz), 7.76 (1H, d, *J*=1.7 Hz), 8.20 (3H, brs), 11.39 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 16.4, 31.7, 57.1, 111.5, 112.7, 113.9, 120.8, 123.9, 125.7, 128.1 135.3, 170.4; MS (ESI) *m/z* 289/287 (M^++1 for the free amino acid). Anal. Calcd for $C_{12}H_{13}BrN_2O_2$·HBr·H_2O: C, 36.39; H, 4.07; N, 7.07. Found: C, 36.27; H, 3.88; N, 7.17.

Cleavage of amino ester 6f by trifluoroacetic acid

(2*S,3*R**)- and (2*S**,3*S**)-β-(2,5-dimethoxy)-phenyltryptophan (7f).** A solution of 300 mg (0.76 mmol) of **6f** in a mixture of TFA (9.5 mL) and water (0.5 mL) was stirred in the presence of Cleland's reagent (6 mg) at room temperature for 3 h. After evaporation of the solvent, the residue was crystallized from ether to give **7f** as trifluoroacetate salt.

(2S,3R*)*-**7f**: yield: 331 mg (96%); amorphous powder; IR (KBr) 3410, 3229, 2953, 1728 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.65 (3H, s), 3.85 (3H, s), 4.74 (1H, d, *J*=9.2 Hz), 5.20 (1H, d, *J*=9.2 Hz), 6.74 (1H, dd, *J*=2.9, 8.8 Hz), 6.86–6.95 (2H, m), 6.98 (1H, t, *J*=8.0 Hz), 7.09 (1H, t, *J*=8.0 Hz), 7.39 (1H, d, *J*=8.0 Hz), 7.48 (1H, d, *J*=8.0 Hz), 7.71 (1H, brs), 8.39 (3H, brs), 11.25 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 36.9, 55.4, 55.8, 56.4, 111.7, 112.3, 112.4, 112.5, 116.5, 118.5, 118.8, 121.5, 123.8, 127.1, 129.2, 136.3, 150.9, 153.2, 170.2; MS (ESI) *m/z* 341 (M^++1 for the free amino acid). Anal. Calcd for $C_{19}H_{20}N_2O_4$·CF_3-COOH·1.5H_2O: C, 52.39; H, 5.03; N, 5.82. Found: C, 52.08; H, 5.31; N, 6.20.

(2S,3S*)*-**7f**: yield: 324 mg (94%); amorphous powder; IR (KBr) 3406, 3239, 2957, 1674 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.63 (3H, s), 3.83 (3H, s), 4.54 (1H, d, *J*=8.3 Hz), 5.11 (1H, d, *J*=8.3 Hz), 6.76 (1H, dd, *J*=3.2, 8.7 Hz), 6.87 (1H, d, *J*=2.8 Hz), 7.06 (1H, t, *J*=7.8 Hz), 7.37 (1H, d, *J*=7.8 Hz), 7.48 (1H, d, *J*=3.2 Hz), 7.90–7.98 (3H, m), 8.30 (3H, brs), 11.14 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 37.8, 55.4, 55.9, 56.2, 111.6, 112.1, 112.2, 112.3, 116.9, 118.5, 118.6, 121.2, 124.1, 127.0, 129.1, 136.1, 150.4, 153.2, 170.9; MS (ESI) *m/z* 341 (M^++1 for the free amino acid). Anal. Calcd for $C_{19}H_{20}N_2O_4$·CF_3-COOH·1.5H_2O: C, 52.39; H, 5.03; N, 5.82. Found: C, 52.65; H, 5.40; N, 6.11.

General procedure for the Pictet–Spengler cyclization of amino esters 6a–c,e,f into tetrahydro-β-carbolines 8a–c,e,f

The mixture of the particular amino ester **6** (110–158 mg, 0.40 mmol), cyclohexanone (1.60–3.50 mmol, 4.0–7.0 equiv.), and, when necessary, a catalytic amount of acetic acid (0.05–0.1 equiv.) was heated at 120°C in dry toluene under nitrogen atmosphere in a Dean-Stark apparatus for 1.5–24 h. The heating was continued until the full consumption of the starting material **6** (TLC monitoring). The solvent was evaporated under reduced pressure, and the residue was submitted to column chromatography (CH_2Cl_2) to give tetrahydro-β-carbolines **8**.

***cis*-(3*S**,4*R**)- and *trans*-(3*S**,4*S**)-4-Methyl-1,2,3,4-tetrahydrospiro[β-carboline-1,1′-cyclohexane]-3-carboxylic acid *tert*-butyl ester (8a).** From **6a**: 110 mg (0.40 mmol), cyclohexanone: 157 mg (1.6 mmol), reflux: 3.5 h [for *cis*-(3*S**,4*R**)-**8a**] or 24 h [for *trans*-(3*S**,4*S**)-**8a**].

cis-(3S,4R*)*-**8a**: yield: 128 mg (90%); oil; IR (film) 3379, 2965, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, d, *J*=6.8 Hz), 1.39–1.96 (10H, m), 1.58 (9H, s), 2.00 (1H, brs), 3.35 (1H, m), 3.85 (1H, d, *J*=4.0 Hz), 7.02–7.18 (2H, m), 7.29 (1H, d, *J*=7.7 Hz), 7.52 (1H, d, *J*=7.7 Hz), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.6, 21.2, 21.4, 25.5, 28.2, 29.9, 34.3, 38.9, 52.3, 56.3, 81.0, 110.6, 113.2, 117.6, 119.1, 121.2, 126.4, 135.7, 140.3, 172.4; MS (EI) *m/z* 354 (M^+), 255; HRMS calcd for $C_{22}H_{30}N_2O_2$ 354.2307. Found: 354.2322. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.67; H, 8.77; N, 7.96.

trans-(3S,4S*)*-**8a**: yield: 89 mg (63%); oil; IR (film) 3415, 3369, 2976, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, d, *J*=6.8 Hz), 1.50–2.01 (11H, m), 1.56 (9H, s), 3.15 (1H, m), 3.30 (1H, d, *J*=9.4 Hz), 7.02–7.18 (2H, m), 7.31 (1H, d, *J*=7.7 Hz), 7.61 (1H, d, *J*=7.7 Hz), 7.85 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.3, 21.1, 21.3, 25.8, 28.2, 32.7, 35.5, 36.3, 51.8, 60.9, 81.1, 110.8, 111.1, 119.2, 119.6, 121.1, 126.9, 135.7, 141.0, 173.3; MS (EI) *m/z* 354 (M^+), 255; HRMS calcd for $C_{22}H_{30}N_2O_2$ 354.2307. Found: 354.2301. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.19; H, 8.65; N, 7.77.

***cis*-(3*S**,4*R**)- and *trans*-(3*S**,4*S**)-4-Isopropyl-1,2,3,4-tetrahydrospiro[β-carboline-1,1′-cyclohexane]-3-carboxylic acid *tert*-butyl ester (8b).** From **6b**: 121 mg (0.40 mmol), cyclohexanone: 157 mg (1.6 mmol), AcOH: 3 mg (0.05 mmol), reflux: 1.5 h [for *cis*-(3*S**,4*R**)-**8b**] or 8 h [for *trans*-(3*S**,4*S**)-**8b**]. The analytical samples were crystallized from ether.

cis-(3S,4R*)*-**8b**: yield: 128 mg (90%); mp 225–227°C; IR (KBr) 3440, 2930, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (3H, d, *J*=5.9 Hz), 1.22 (3H, d, *J*=5.9 Hz), 1.57 (9H, s), 1.59–1.90 (10H, m), 1.99 (1H, m), 2.13 (1H, brs), 3.21 (1H, dd, *J*=2.9, 3.5 Hz), 3.78 (1H, d, *J*=3.5 Hz), 7.09 (1H, t, *J*=7.7 Hz), 7.14 (1H, t, *J*=7.7 Hz), 7.32 (1H, d, *J*=7.7 Hz), 7.56 (1H, d, *J*=7.7 Hz), 7.79 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.2, 21.6, 25.3, 25.4, 28.2, 30.2, 34.3, 38.2, 41.3, 52.6, 58.1, 81.0, 110.1, 110.6, 119.1, 119.5, 121.0, 128.1, 135.8, 141.3, 172.8; MS (EI) *m/z* 382 (M^+), 283, 195, 182; HRMS calcd for $C_{24}H_{34}N_2O_2$ 382.2620. Found: 382.2633. Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.36; H, 8.96; N, 7.32. Found: C, 75.02; H, 9.15; N, 7.23.

trans-(3S,4S*)*-**8b**: yield: 99 mg (65%); 227–229°C; IR (KBr) 3385, 2932, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=5.9 Hz), 1.07 (3H, d, *J*=5.9 Hz), 1.43 (9H, s), 1.52–1.97 (11H, m), 2.45 (1H, m), 3.35 (1H, t, *J*=5.8 Hz), 3.68 (1H, d, *J*=5.8 Hz), 7.00 (1H, t, *J*=7.7 Hz), 7.12 (1H, t, *J*=7.7 Hz), 7.30 (1H, d, *J*=7.7 Hz), 7.58 (1H, d, *J*=7.7 Hz), 7.83 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.7, 21.4, 21.4, 21.5, 25.8, 27.9, 30.8, 37.2, 38.0, 40.9, 51.6, 55.3, 80.6, 109.9, 110.6, 119.1, 119.6, 121.0, 127.6, 135.7, 141.3, 174.2; MS (EI) *m/z* 382 (M^+), 283, 238, 195, 182; HRMS calcd for $C_{24}H_{34}N_2O_2$ 382.2620. Found: 382.2625. Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.36; H, 8.96; N, 7.32. Found: C, 75.65; H, 9.05; N, 7.08.

***cis*-(3*S**,4*R**)- and *trans*-(3*S**,4*S**)-4-(3-Pentyl)-1,2,3,4-tetrahydrospiro[β-carboline-1,1′-cyclohexane]-3-carboxylic acid *tert*-butyl ester (8c).** From **6c**: 132 mg (0.40 mmol), cyclohexanone: 157 mg (1.6 mmol), reflux: 5 h [for *cis*-(3*S**,4*R**)-**8c**] or 4.5 h [for *trans*-(3*S**,4*S**)-**8c**]. The analytical samples were crystallized from ether.

cis-(3S,4R*)*-**8c**: yield: 161 mg (98%); mp 166–167°C; IR (KBr) 3379, 2959, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (3H, t, *J*=6.8 Hz), 1.03 (3H, t, *J*=6.8 Hz), 1.10–1.82 (15H, m), 1.48 (9H, s), 2.00 (1H, m), 3.34 (1H, dd, *J*=3.6, 3.8 Hz), 3.72 (1H, d, *J*=3.8 Hz), 6.94–7.07 (2H, m), 7.21 (1H, d, *J*=7.7 Hz), 7.43 (1H, d, *J*=7.7 Hz), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.4, 21.2, 21.6, 24.9, 25.4, 25.9, 28.1, 34.2, 37.0, 38.6, 43.7, 52.5, 58.1, 81.0, 110.5, 110.7, 119.0, 119.2, 120.9, 127.7, 135.8, 141.4, 172.7; MS (EI) *m/z* 410 (M^+), 311, 281, 238, 195, 182; HRMS calcd for $C_{26}H_{38}N_2O_2$ 410.2935. Found: 410.2933. Anal. Calcd for $C_{26}H_{38}N_2O_2$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.76; H, 9.65; N, 6.83.

trans-(3S,4S*)*-**8c**: yield: 117 mg (71%); mp 145–146°C; IR (KBr) 3380, 2959, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (3H, t, *J*=6.8 Hz), 0.98 (3H, t, *J*=6.8 Hz), 1.03–1.85 (15H, m), 1.38 (9H, s), 1.90 (1H, m), 3.54 (1H, dd, *J*=6.5, 6.6 Hz), 3.73 (1H, d, *J*=6.6 Hz), 6.92–7.08 (2H, m), 7.21 (1H, d, *J*=7.8 Hz), 7.51 (1H, d, *J*=7.8 Hz), 7.86 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.5, 12.9, 21.4, 23.2, 24.0, 25.9, 27.0, 27.9, 36.9, 37.5, 37.6, 44.5, 51.5, 55.5, 80.6, 109.6, 110.6, 118.9, 119.6, 120.9, 127.3, 135.7, 141.6, 174.1; MS (EI) *m/z* 410 (M^+), 309, 238, 195, 182; HRMS calcd for $C_{26}H_{38}N_2O_2$ 410.2935. Found: 410.2940. Anal. Calcd for $C_{26}H_{38}N_2O_2$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.96; H, 9.50; N, 7.01.

***cis*-(3*S**,4*R**)- and *trans*-(3*S**,4*S**)-4-Phenyl-1,2,3,4-tetrahydrospiro[β-carboline-1,1′-cyclohexane]-3-carboxylic acid *tert*-butyl ester (8e).** From **6e**: 134 mg (0.40 mmol), cyclohexanone: 275 mg (2.8 mmol), AcOH: 3 mg (0.05 mmol), reflux: 10 h [for *cis*-(3*S**,4*R**)-**8e**] or 7 h [for *trans*-(3*S**,4*S**)-**8e**]. The analytical samples were crystallized from methanol or ether.

cis-(3S,4R*)*-**8e**: yield: 150 mg (90%); mp 219.5–221°C (dec) (methanol); IR (KBr) 3370, 2928, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (9H, s), 1.48–2.07 (11H, m), 4.13 (1H, d, *J*=4.5 Hz), 4.45 (1H, d, *J*=4.5 Hz), 6.94 (1H, t, *J*=7.4 Hz), 7.07 (1H, t, *J*=7.4 Hz), 7.12–7.28 (6H, m), 7.36 (1H, d, *J*=7.4 Hz), 7.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.5, 25.6, 28.0, 34.3, 39.0, 41.7, 52.2, 57.2, 81.2, 110.6, 110.9, 118.4, 119.4, 121.5, 126.6, 126.7, 127.8, 129.4, 135.8, 140.8, 141.1, 171.1; MS (EI) *m/z* 416 (M^+), 360, 315, 287; HRMS calcd for $C_{27}H_{32}N_2O_2$ 416.2464. Found: 416.2455. Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.72. Found: C, 77.49; H, 7.61; N, 6.66.

trans-(3S,4S*)*-**8e**: yield: 148 mg (89%); mp 209–210°C (ether); IR (KBr) 3402, 2926, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (9H, s), 1.46–2.15 (11H, m), 3.64 (1H, d, *J*=9.8 Hz), 4.17 (1H, d, *J*=9.8 Hz), 6.52 (1H, d, *J*=8.0 Hz), 6.77 (1H, t, *J*=8.0 Hz), 7.03 (1H, t, *J*=8.0 Hz), 7.15–7.31 (6H, m), 7.90 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.3, 25.8, 27.9, 35.9, 38.5, 46.2, 52.1, 61.6, 81.0, 110.0, 110.5, 119.1, 119.8, 121.2, 126.6, 126.7, 128.2, 128.9, 135.6, 141.7, 141.8, 172.6; MS (EI) *m/z* 416 (M^+), 360, 315, 287; HRMS calcd for $C_{27}H_{32}N_2O_2$ 416.2464. Found: 416.2468. Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.72. Found: C, 78.06; H, 8.05; N, 6.38.

***trans*-(3*S**,4*R**)- and *cis*-(3*S**,4*S**)-4-(2,5-Dimethoxyphenyl)-1,2,3,4-tetrahydrospiro[β-carboline-1,1′-cyclohexane]-3-carboxylic acid *tert*-butyl ester (8f).** From **6f**: 158 mg (0.40 mmol), cyclohexanone: 275 mg (2.8 mmol), reflux: 5 h [for *trans*-(3*S**,4*R**)-**8f**] or 7 h [for *cis*-(3*S**,4*S**)-**8f**]. The analytical samples were crystallized from ether.

trans-(3S,4R*)*-**8f**: yield: 162 mg (85%); mp 208–210°C; IR (KBr) 3433, 3339, 2928, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (9H, s), 1.43–2.13 (11H, m), 3.62 (6H, brs), 3.87 (1H, d, *J*=9.1 Hz), 4.58 (1H, d, *J*=9.1 Hz), 6.55–6.87 (5H, m), 7.00 (1H, t, *J*=8.0 Hz), 7.22 (1H, d, *J*=8.0 Hz), 7.90 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.3, 25.9, 27.8, 31.5, 35.8, 38.4, 52.0, 55.6, 58.1, 59.4, 80.6, 110.2, 110.4, 111.7, 111.9, 116.4, 119.0, 119.3, 120.9, 126.7, 131.7, 135.6, 141.0, 152.3, 153.7, 172.6; MS (EI) *m/z* 476 (M^+), 420, 375, 347; HRMS calcd for $C_{29}H_{36}N_2O_4$ 476.2675. Found: 476.2671. Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 73.33; H, 7.42; N, 5.93.

cis-(3S,4S*)*-**8f**: yield: 168 mg (88%); mp 142–143°C; IR (KBr) 3433, 3339, 2928, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (9H, s), 1.40–2.01 (10H, m), 2.30 (1H, d, *J*=6.8 Hz), 3.63 (3H, s), 3.91 (3H, s), 4.11 (1H, dd, *J*=4.8, 6.8 Hz), 5.02 (1H, d, *J*=4.8 Hz), 6.62 (1H, dd, *J*=2.7, 8.2 Hz), 6.75 (1H, d, *J*=8.2 Hz), 6.94 (1H, t, *J*=7.8 Hz), 7.05 (1H, t, *J*=7.8 Hz), 7.17 (1H, d, *J*=7.8 Hz), 7.25 (1H, d, *J*=2.7 Hz), 7.34 (1H, d, *J*=7.8 Hz), 8.00 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.5, 25.5, 27.6, 32.2, 34.0, 38.7, 51.9,

55.3, 55.6, 56.7, 80.6, 110.3, 110.5, 111.2, 111.5, 116.7, 118.6, 119.1, 121.3, 126.7, 131.5, 135.8, 140.8, 151.2, 153.0, 171.3; MS (EI) *m/z* 476 (M^+), 420, 375, 347; HRMS calcd for $C_{29}H_{36}N_2O_4$ 476.2675. Found: 476.2673. Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 73.24; H, 7.32; N, 5.86.

Acknowledgements

We thank Ph. Sigaut (MS, EI), P. Szabo (A. Szent-Györgyi Medical University, Szeged, Hungary, MS, ESI), D. Royer and C. Peterman (NMR) for spectroscopic measurements. Financial support by ADIR and Co. (Laboratoires Servier) is gratefully acknowledged.

References

1. Reviews, see: (a) Rizo, J.; Gierasch, L. M. *Annu. Rev. Biochem.* **1992**, *61*, 387. (b) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845. (c) McDowell, R. S.; Artis, D. R. *Ann. Rep. Med. Chem.* **1995**, *30*, 265. (d) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolym. (Pept. Sci.)* **1997**, *43*, 219. For some selected, recent references, see: (e) Sagan, S.; Josien, H.; Karoyan, P.; Brunissen, A.; Chassaing, G.; Lavielle, S. *Bioorg. Med. Chem.* **1996**, *4*, 2167. (f) Salvadori, S.; Balboni, G.; Guerrini, R.; Tomatis, R.; Bianchi, C.; Bryant, S. D.; Cooper, P. S.; Lazarus, L. H. *J. Med. Chem.* **1997**, *40*, 3100. (g) Tourwé, D.; Mannekens, E.; Thi Diem, T. N.; Verheyden, P.; Jaspers, H.; Tóth, G.; Péter, A.; Kertész, I.; Török, G.; Chung, N. N.; Schiller, P. W. *J. Med. Chem.* **1998**, *41*, 5167. (h) Tóth, K.; Kovács, M.; Zarándi, M.; Halmos, G.; Groot, K.; Nagy, A.; Kele, Z.; Schally, A. V. *J. Pept. Res.* **1998**, *51*, 134.

2. (a) Ramachandran, G. N.; Sasisekharan, V. *Adv. Protein Chem.* **1968**, *23*, 283. (b) Scherega, H. A. *Chem. Rev.* **1971**, *71*, 195.

3. (a) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. (b) Gibson (née Thomas), S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron*, **1999**, *55*, 585, and references cited therein.

4. Fontana, A.; Toniolo, C. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 309.

5. (a) Huang, Z.; He, Y.-B.; Raynor, K.; Tallent, M.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1992**, *114*, 9390. (b) Haskell-Luevano, C.; Boteju, L.; Miwa, H.; Dickinson, C.; Gantz, I.; Yamada, T.; Hadley, M. E.; Hruby, V. J. *J. Med. Chem.* **1995**, *38*, 4720. (c) Haskell-Luevano, C.; Toth, K.; Boteju, L.; Job, C., de L. Castrucci, A. M.; Hadley, M. E.; Hruby, V. J. *J. Med. Chem.* **1997**, *40*, 2740. (d) Bonner, G. G.; Davis, P.; Stropova, D.; Edsall, S.; Yamamura, H. L.; Porreca, F.; Hruby, V. J. *J. Med. Chem.* **2000**, *43*, 569.

6. Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462.

7. Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 77.

8. Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C. H.; Moews, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595.

9. Snyder, H. R.; Matteson, D. S. *J. Am. Chem. Soc.* **1957**, *79*, 2217.

10. Erofeev, Y. V.; Velezheva, V. S.; Genkina, N. K.; Suvorov, N. N. *Khim. Geterosikl. Soedin.* **1978**, *6*, 780.

11. Neef, G. G.; Eder, U.; Huth, A.; Rahtz, D. *Heterocycles* **1983**, *20*, 1295.

12. (a) Behforouz, M.; Zarrinmayeh, H.; Ogle, M. E.; Riehle, T. J.; Bell, F. W. *J. Heterocycl. Chem.* **1988**, *25*, 1627. (b) Spöndlin, C.; Tamm, C. *Heterocycles* **1989**, *28*, 453.

13. (a) Boteju, L. W.; Wegner, K.; Qian, X.; Hruby, V. J. *Tetrahedron* **1994**, *50*, 2391. (b) Bruncko, M.; Crich, D. *J. Org. Chem.* **1994**, *59*, 4239. (c) Shapiro, G.; Buechler, D.; Marzi, M.; Schmidt, K.; Gomez-Lor, B. *J. Org. Chem.* **1995**, *60*, 4978.

14. Horwell, D. C.; McKiernan, M. J.; Osborne, S. *Tetrahedron Lett.* **1998**, *39*, 8729.

15. Gong, Y.; Kato, K.; Kimoto, H. *Tetrahedron Lett.* **1999**, *40*, 5743.

16. (a) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434. (b) Rodriguez, R.; Vinets, I.; Diez, A.; Rubiralta, M. *Synth. Commun.* **1996**, *26*, 3029. (c) Damour, D.; Pulicani, J.-P.; Vuilhorgne, M.; Mignani, S. *Synlett*, **1999**, 786.

17. Jeannin, L.; Nagy, T.; Vassileva, E.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 2057.

18. For a review on the chemistry of Meldrum's acid, see: Chen, B.-C. *Heterocycles* **1991**, *32*, 529.

19. Oikawa, Y.; Hirasawa, O.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759.

20. Ring opening of **2e** with different alcohols (MeOH, EtOH, *i*-PrOH, *t*-BuOH) was completely non-selective, while using benzyl or allyl alcohol a weak diasteroselectivity (d.e. 44 and 20%, respectively) was observed, probably due to π stacking interactions. For a review see, Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.

21. Ninomiya, N.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

22. Nagy, T.; Jeannin, L.; Sapi, J.; Laronze, J.-Y.; Renard, P.; Pfeiffer, B.; Bizot-Espiard, J.-G. *Eur. J. Med. Chem.* **1995**, *30*, 575.

23. Computational results in the form of *Z*-matrices with the computed total energies, as supporting information, are available on request (F. A.)

24. DISCOVER® Molecular Simulation, Inc., 9685 Scranton Road, San Diego, CA 92121-4778, 1998.

25. (a) Maple, J. R.; Dinur, U.; Hagler, A. T. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 5350. (b) Maple, J. R.; Hwang, M.-J.; Stockfish, T. P.; Dinur, U.; Waldman, M.; Ewig, C. S.; Hagler, A. T. *J. Comput. Chem.* **1994**, *15*, 162.

26. Dewar, M. S. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

27. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr., Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. GAUSSIAN98, Revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

28. Rinaldi, D.; Hoggan, P. E.; Cartier, A. The GEOMOS program; QCPE 584a, *QCPE Bull.* **1989**, 128.

29. For the resolution and characterization of the absolute configuration of β-substituted tryptophans (**7a**,**b**,**c**,**e**,**f**) analytical

HPLC methods have already been developed: (a) Péter, A.; Török, G.; Tóth, G.; Tourwé, D.; Mannekens, E.; Van Den Nest, W.; Sapi, J.; Armstrong, D.W. *Peptides* **1998**, Proceedings of the 25th European Peptide Symposium, Bajusz, S.; Hudecz, F.; Eds.; Wiley: New York, 1999; pp 300–301. (b) Péter, A.; Péter, M.; Fülöp, F.; Török, G.; Tóth, G.; Tourwé, D.; Sapi, J. *Chromatographia* **2000**, *51*, 148–154. (c) Török, G.; Péter, A.; Vékes, E.; Sapi, J.; Laronze, M.; Laronze, J.-Y.; Armstrong, D. W. *Chromatographia* **2000**, *51*, 165–174.

30. For designation of the relative configurations for the compounds containing two chiral centers, we utilized the configurational descriptors R^* and S^* as in the literature the use of other nomenclatures (e.g. *erythro-threo*) for the configurational notation is not only confusing but in certain cases incorrect as well.