129. A New General Approach to Enantiomerically Pure Cyclic and Open-Chain (*R*)- and (*S*)-α,α-Disubstituted α-Amino Acids

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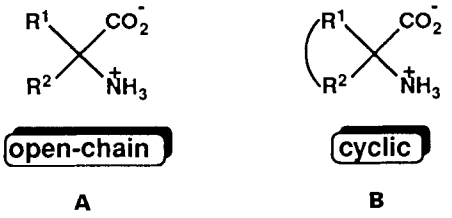
A wide range of cyclic and open-chain α,α-disubstituted α-amino acids **1a–p** were prepared. The racemic *N*-acylated α,α-disubstituted amino acids were resolved by coupling to chiral amines **15–18** derived from (*S*)-phenylalanine to form diastereoisomers **19/20** or **21/22** that could be separated by crystallization and/or flash chromatography on silica gel (*Scheme 3*). Selective cleavage *via* the 1,3-oxazol-5(4*H*)-ones **10a–p** gave the corresponding optically pure α,α-disubstituted amino-acid derivatives **11** or **12** in high yield (*Scheme 3*). The aboslute configurations of the α,α-disubstituted amino acids were determined from X-ray structures of the diastereoisomers **20**, **21g'**, **22d**.

Introduction. – There is an ever-growing interest in the synthesis, pharmacology, and conformational properties of non-proteinogenic amino acids. In particular, α,α-disubstituted α-amino acids of type **A** or **B** were the subject of numerous investigations over recent years. A large number of these studies focused on α-aminoisobutyric acid (= 2-amino-2-methylpropanoic acid; Aib) [1] and (−)-(*R*)-2-amino-2-methylbutyric acid (D-Iva) [2], which are the main naturally occurring members of this family. These amino acids are important constituents of a class of microbial peptide antibiotics, known as the peptaibols [3]. The presence of α,α-disubstituted amino acids in these peptides is thought to play a crucial role in their ability to form trans-membrane helical ion channels. Conformational-energy calculations and numerous X-ray studies have highlighted the effect of these unusual amino acids on peptide conformation and shown that the nature of the substituents R^1 and R^2 of amino acids of type **A** or **B** is of great importance. It is now

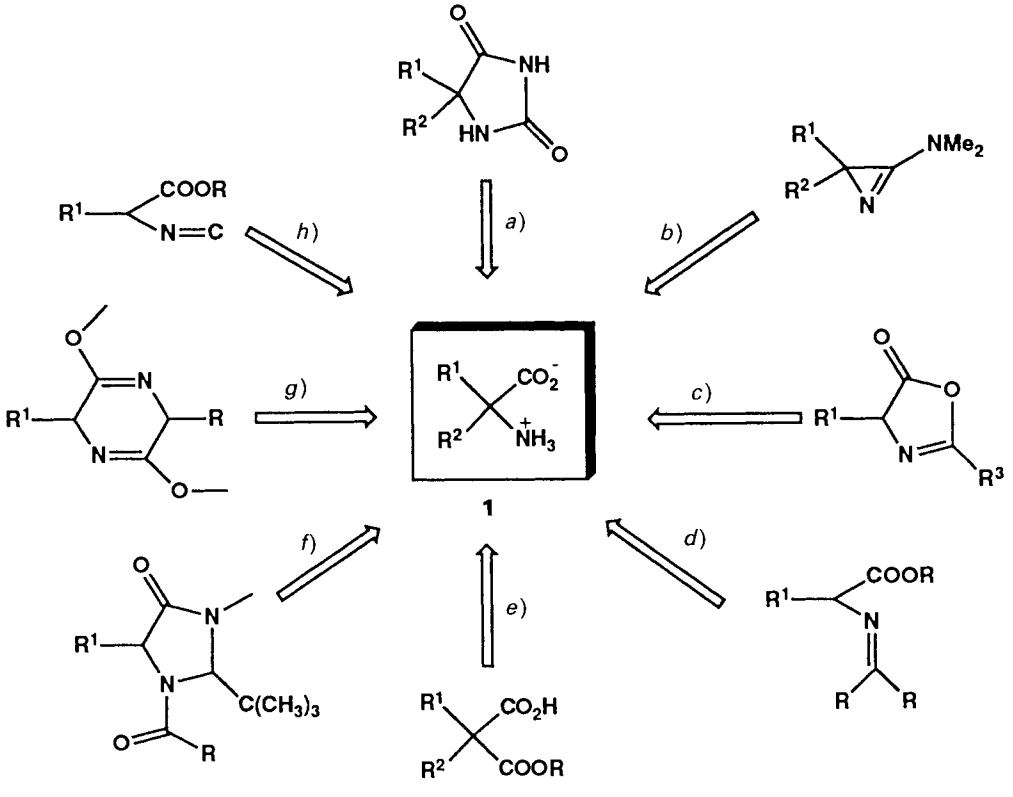


[1]) Part of the Ph. D. Thesis of *C. S.*, University of Zürich, 1992.

generally agreed, that Aib and α,α-disubstituted amino acids with a Me group at the α-position, tend to induce 3_{10}- or α-helical conformations when incorporated into peptides [4]. This is also true for certain cyclic α,α-disubstituted amino acids, notably those with 3-, 5-, and 6-membered rings [5]. However, in the acyclic series, two side-chains larger than Me at C(α) tend to induce more extended structures [6].

Racemic and enantiomerically pure α,α-disubstituted amino acids were prepared by a number of different routes, some of which are indicated in *Scheme 1*: *a*) by hydrolysis of hydantoins obtained from the *Bucherer* reaction [7] (symmetrical and asymmetrical *Strecker* reactions were also used); *b*) by reaction of 3-amino-2*H*-azirines with carboxylic acids yielding, after rearrangement, *N*-acylated amino-acid amides which can then be selectively deprotected [8]; *c*) by cyclization of *N*-acylated mono-substituted amino acids to 1,3-oxazol-5(4*H*)-ones [9], which can then be alkylated at the α-position and hydrolysed to the free amino acid; *d*) by alkylation of imines [10], followed by cleavage of the auxiliary (often chiral); *e*) by the *Schmidt* rearrangement on disubstituted mono-esters of malonic acid [11], followed by hydrolysis; *f*) by diastereoselective enolate alkylation of imidazolidin-4-ones [12] (one class of *Seebach*'s 'chiral glycines'); *g*) by metalla-

Scheme 1

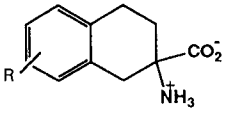


a)–*h*) See text.

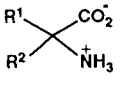
tion and subsequent alkylation of *Schöllkopf*'s bis-lactim ethers [13], providing, after hydrolysis under mild acidic conditions, a wide range of α,α-disubstituted amino acids; *h*) finally, by alkylation of substituted isonitriles [14].

For reasons that are outside the scope of this communication, we are interested in both enantiomers of these novel non-proteinogenic amino acids. Hence, an efficient method for the resolution of the racemic amino acids would be more practical than an enantioselective synthesis. For the preparation of open-chain racemic α,α-disubstituted amino acids, the most practical of the routes shown in *Scheme 1* are probably *a*), *b*), and *c*), which proceed *via* the hydantoin, 3-amino-2*H*-azirine, and 1,3-oxazol-5(4*H*)-one, respectively. However, if cyclic analogues of these amino acids are also required (especially for the tetralin and indane amino acids), then proceeding *via* the hydantoin is probably the method of choice.

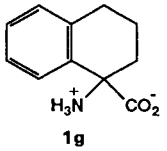
In this paper, we present a very efficient strategy for the preparation and resolution of both acyclic and cyclic *N*-acylated α,α-disubstituted amino acids, *i.e.* of *N*-acylated derivatives of **1a–p**. The method is based on the observation that certain diastereoisomeric di- and tripeptides derived from these *N*-acylated amino acids and chiral amines containing one or two (*S*)-phenylalanine residues are easily separated by flash chromatography (FC) [15] using solvent mixtures of Et_2O and i-PrOH [16]. Once separated, these diastereoisomers are selectively cleaved to give either acylated amino acids or esters in high yield. Furthermore, the chiral amines can be routinely recovered in 70–80% after cleavage. We found that the longer tripeptides routinely are separated best and quite often give diastereoisomers that crystallize in optically pure form.



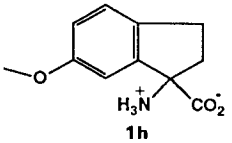
1a R = H
b R = 5-MeO
c R = 6-MeO
d R = 7-MeO
e R = 8-MeO
f R = 6,7-$(MeO)_2$



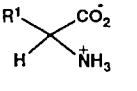
1i R^1 = Me, R^2 = 4-MeO-$C_6H_4CH_2$
k R^1 = Me, R^2 = *t*-Bu
l R^1 = Me, R^2 = cyclo-Pr
m R^1 = Me, R^2 = i-Pr
n R^1 = Me, R^2 = Ph
o R^1 = allyl, R^2 = Ph
p R^1 = Me, R^2 = $PhCH_2$



1g



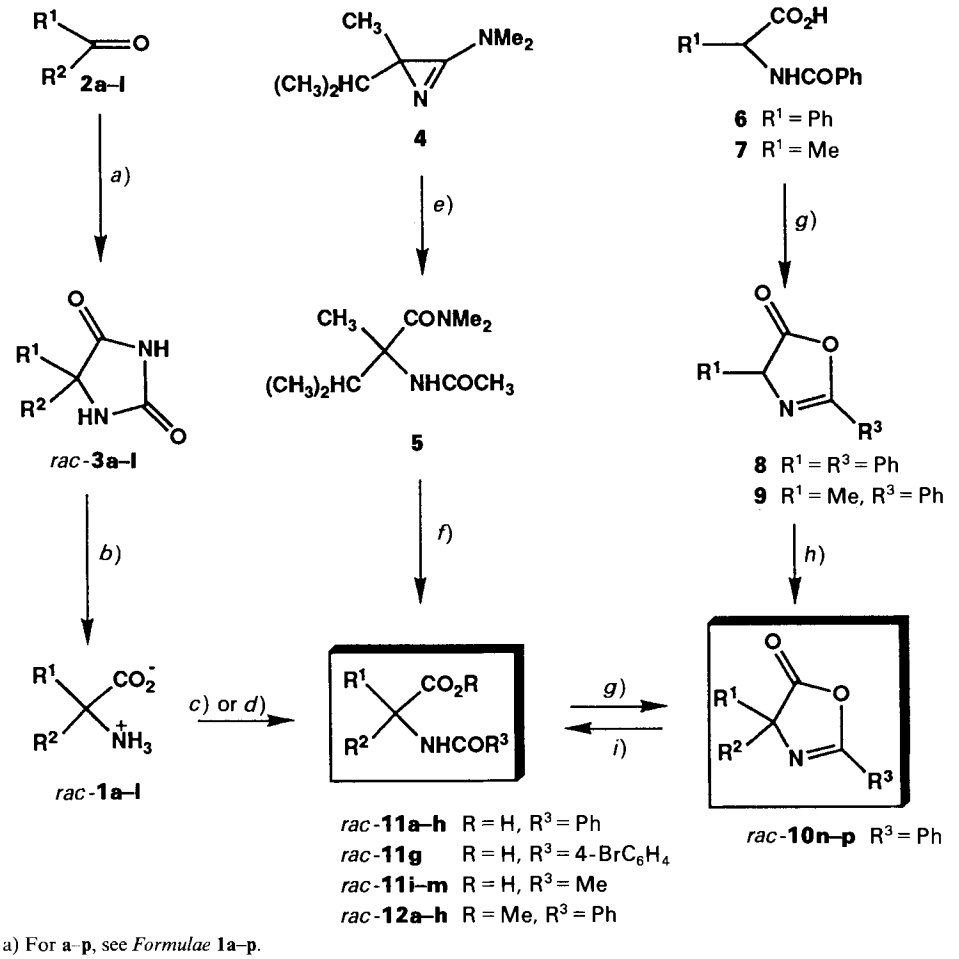
1h



1q R^1 = i-Pr, valine
r R^1 = $PhCH_2$, phenylalanine

Synthesis of *N*-Acylated α,α-Disubstituted Amino Acids. – *Cyclic Amino Acids.* Diastereospecific syntheses [12] [13] of optically pure cyclic α,α-disubstituted amino acids are in general not practical. Therefore, it seemed especially interesting to apply our methodology to this class of compounds. We focused our attention on the α- and β-tetralin- and α-indane-derived amino acids *rac*-**1a–h** (see above), since they represent conformationally constrained phenylalanine and tyrosine analogues and presumably

Scheme 2[a])



a) For **a**–**p**, see *Formulae* **1a**–**p**.

a) KCN, $(NH_4)_2CO_3$, EtOH/H_2O, Δ (*Methods A* and *B*). *b*) $Ba(OH)_2$, H_2O, Δ (*Method C*). *c*) NaOH, R^3COCl (R^3 = Ph for **a**–**h**, R^3 = 4-BrC_6H_4 for **g'**) (*Method D*). *d*) Ac_2O, pyridine, Δ (*Method E*) for R^3 = Me. *e*) MeCN, AcOH, r.t. *f*) HCl, MeCN/H_2O, 70°. *g*) DCC, CH_2Cl_2, r.t. *h*) $(i\text{-Pr})_2EtN$, DMF, R^2X, Δ (*Method F*). *i*) HCl, H_2O/dioxane for R = H (*Method L*); HCl (g), MeOH for R = Me (*Method M*).

have α-helix-stabilizing properties [19]. We followed the route *via* the hydantoins *rac*-**3** outlined in *Scheme 2*, as most of the starting ketones **2** were commercially available. In addition, it seemed desirable to try and extend this route to provide a general method for the synthesis of both cyclic and acyclic optically pure α,α-disubstituted amino acids.

In the β-tetralin series, amino acids *rac*-**1a**–**f** were synthesized from the corresponding ketones **2a**–**f**. Whereas **2a, c, d, f** were commercially available, 5-methoxy-β-tetralone **2b** was prepared according to [20][2]), and 8-methoxy-β-tetralone **2e** was obtained by *Birch*

[2]) The experiment given in [20] for 8-methoxy-β-tetralone gives the 5-methoxy- and not the 8-methoxy-β-tetralone.

reduction [21] of 1,7-dimethoxynaphthalene. Since these β-tetralones were generally not very stable, they were isolated as their hydrogen-sulfite adducts, which could be used directly in the *Bucherer* reaction. Thus, the β-tetralin hydantoins *rac*-**3a–f** were synthesized from **2a–f** and then hydrolyzed with $Ba(OH)_2$ using conditions slightly modified from those described [17] (*Methods A* and *C*). For the commercially available unsubstituted α-tetralone **2g** and 6-methoxy-α-indanone **2h**, slightly harsher conditions were necessary to achieve good yields of *rac*-**3g** and *rac*-**3h**, respectively (*Method B*). Hydrolysis with $Ba(OH)_2$ to the corresponding amino acids *rac*-**1g** and *rac*-**1h** was accomplished in a straightforward manner.

Early attempts to N^2-benzoylate[3]) the cyclic α,α-disubstituted amino acids *rac*-**1a–h** using the classical *Schotten-Baumann* method [18] gave only moderate yields. Changing the solvent (*e.g.* DMF and pyridine) and using a variety of different reaction conditions (*e.g.* different temperatures and addition of 4-(dimethylamino)pyridine) even worsened the results. The problems with the *Schotten-Baumann* approach were finally solved reproducibly by using vigorous stirring throughout the reaction and by addition of an extra equiv. of benzoyl chloride. This latter point is important, as part of the acylating reagent was consumed by anhydride formation, which was immediately followed by intramolecular cyclization to the 1,3-oxazol-5(4*H*)-one. This side reaction could not be avoided, but the crude product mixture was saponified to afford the N^2-benzoylated amino acids *rac*-**11a–h** (R^3=Ph) in high yield. In the case of *rac*-**1g**, acylation with 4-bromobenzoyl chloride gave *rac*-**11g′**, which was used in the resolution step to obtain X-ray-quality crystals of the corresponding diastereoisomers (see below).

Acyclic Amino Acids. In [16], we described the synthesis of the acyclic amino acids *rac*-**1i–p**. Three strategies (*Scheme 2*) were used to get to their corresponding *N*-acylated amino acids and *rac*-1,3-oxazol-5(4*H*)-ones *rac*-**11i–m** and *rac*-**10n–p**. The choice of the method depended largely on the availability of the intermediates. The amino acids *rac*-**1i–l** were synthesized from the commercially available ketones **2i–l** *via* the hydantoins *rac*-**3i–l** as described above for the cyclic amino acids (*Methods A* and *C*). The amino acids were generally isolated by precipitation from aqueous solution at neutral pH. The next step was N^α-acetylation to *rac*-**11i–l** (R^3=Me) using Ac_2O/pyridine. The acetylated derivative *rac*-**11m** (R^3=Me) of amino acid **1m** was synthesized from 3-amino-2*H*-azirine **4** and AcOH *via* a rearrangement (→ **5**), followed by selective hydrolysis under mild conditions. Finally, the benzoylated mono-substituted amino acids[3]) **6** and **7** were converted into their corresponding dialkylated 1,3-oxazol-5(4*H*)-ones *rac*-**10n–p** (R^3=Ph), using the literature procedure [9], *i.e.* the mono-substituted 1,3-oxazol-5(4*H*)-ones **8** and **9** were alkylated with either MeI, $PhCH_2Br$, or allyl bromide in the presence of diisopropylethylamine ($(i\text{-}Pr)_2EtN$) in high yield. If required, the 1,3-oxazol-5(4*H*)-ones *rac*-**10** could be converted to the *N*-acylated amino acids *rac*-**11** or the methyl esters *rac*-**12**. The reverse reaction was accomplished by treating the *N*-acylated amino acids with *N*,*N*′-dicyclohexylcarbodiimide (DCC) at 0°.

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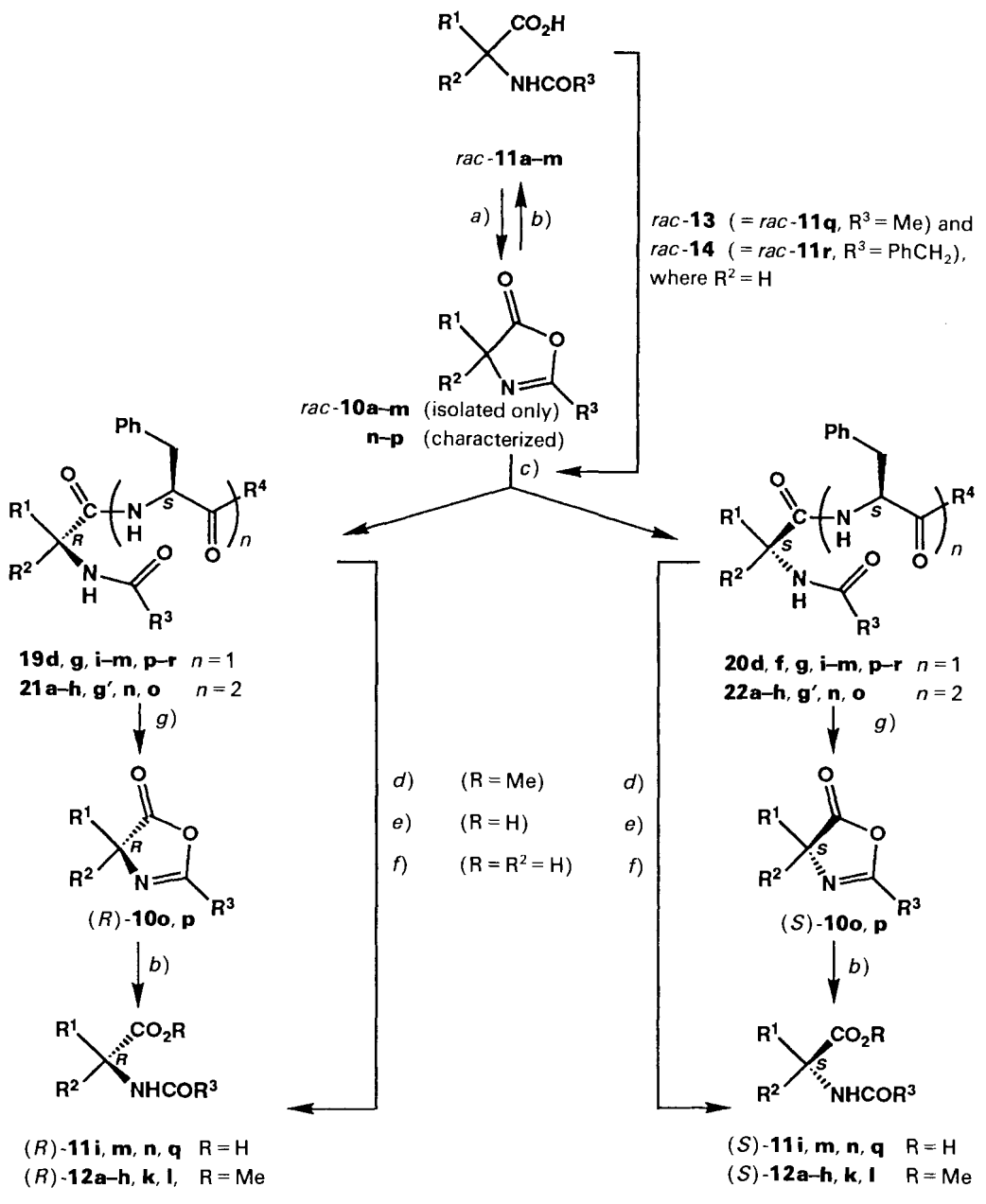
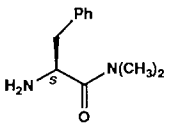
[3]) It was found that the 2-phenyl-1,3-oxazol-5(4*H*)-ones *rac*-**10** (R^3 = Ph; see below), used for the resolution with one of the chiral amines **15–18**, gave only traces of the undesired imidazolidin-4-ones in that step, in contrast to the corresponding acetylated derivatives. Also the N^2-benzoylated amino acids were preferred for the better crystallinity and separation of the corresponding diastereoisomers.

Scheme 3[a])



a) For **a**–**r**, see *Formulae* **1a**–**r**.

a) CDI/THF, CDI/CH_2Cl_2, DCC/CH_2Cl_2, or Ac_2O, Δ (*Methods G–I*). *b*) Aq. HCl soln./dioxane. *c*) DMF, **15**–**18**, 50–80° (*Method H*). *d*) 15% HCl (g)/MeOH, 80° (*Method M*) or CF_3SO_3H, MeOH, 80° (*Method N*) for R = Me. *e*) 4N aq. HCl soln./dioxane 1:1, 80° (*Method L*) or HCl (g), MeCN/H_2O 4:1, 70–90° for R = H. *f*) 16% HBr (g), $MeNO_2/H_2O$, 70° (*Method O*) for R = R^1 = H. *g*) HCl (g), toluene, 80° (*Method K*).



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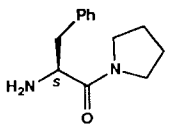

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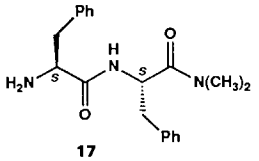

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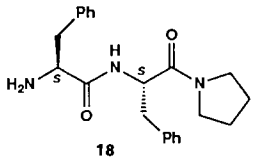

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Resolution of α,α-Disubstituted *N*-Acylated Amino Acids. – Cyclization of both the open-chain and cyclic *N*-acylated α,α-disubstituted amino acids *rac*-**11** to the 1,3-oxazol-5(4*H*)-ones *rac*-**10** was performed with a variety of different activating agents (*Scheme 3*). In most cases, the disubstituted 1,3-oxazol-5(4*H*)-ones were isolated as stable colorless solids (not characterized), in contrast to their mono-substituted analogues. In a few examples, when 1,1′-carbonyldiimidazole (CDI) was used (*Method G*), the 1,3-oxazol-5(4*H*)-ones were not isolated, and the chiral amine used for the formation of the diastereoisomers was added directly to the reaction mixture[4]).

The best conditions for coupling the 1,3-oxazol-5(4*H*)-ones *rac*-**10** to the chiral amines **15**–**18** involved heating the two components together in DMF at 50° for *ca.* 24 h (*Scheme 3*). Such conditions could be employed, as there was no risk of epimerization due to dialkylation at the α-position. Reaction times were found, in general, to be slightly longer for the α-tetralin- and α-indane-derived amino-acid derivatives, probably due to a slight increase in steric hindrance around their C(α) atoms. At the beginning of this study, we mainly used chiral amines **15** and **16** containing only one (*S*)-phenylalanine residue. These gave the diastereoisomeric dipeptides of type **19** and **20**. As the study progressed, the chiral amines **17** and **18** containing two (*S*)-phenylalanine moieties were used preferentially, due to the improved separation of the diastereoisomeric tripeptides of type **21** and **22**. All diastereoisomeric di- and tripeptides **19**–**22** were colorless solids. Often, one of the diastereoisomers could be selectively crystallized after workup (normally the *most* polar one of the two), which *more* simplified the chromatographic separation when working on large scale. The FC separation (silica gel) of the diastereoisomers was normally a straightforward matter, due to the large differences in their R_f values (*Tables 1–3*). The choice of the proper eluent was, however, fairly critical. Best results were generally obtained using mixtures of i-PrOH/Et_2O.

It was possible to obtain X-ray-quality crystals from diastereoisomers **20f** (see *Exper. Part*) and **22d** in the β-tetralin series and **21g′** in the α-tetralin series (*Figs. 1–3*) by slow evaporation of AcOEt/hexane and MeOH solutions, respectively. Structure determination of these α- and β-tetralin derivatives, making use of the known configuration of the (*S*)-configurated Phe building block, allowed us to establish the (*S*)-configuration at the C(α)-atoms of the nonproteinogenic amino acids **20f** and **22d**. In both cases, these were the more polar of the two diastereoisomers. In the less polar diastereoisomer **21g′** containing the unsubstituted α-tetralin-derived amino acid, the absolute configuration at the disubstituted α-position was found to be (*R*) by X-ray structure determination.

Several methods were used to selectively cleave the chiral amines from the N^2-acylated α,α-disubstituted amino-acid amides **19**–**22**, all proceeding *via* the 1,3-oxazol-5(4*H*)-ones

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[4]) For the coupling of the α-mono-substituted N^2-acetylvaline (*rac*-**13**; from valine (*rac*-**1q**)); N^2-(phenylacetyl)phenylalanine (*rac*-**14**; from phenylalanine (*rac*-**1r**)) to the chiral amine **15**, *Method G* was also used. However, in this case, the reaction did not proceed *via* the 1,3-oxazol-5(4*H*)-one.

Table 1. *Synthesis of Dipeptides* **19** *and* **20** *and Tripeptides* **21** *and* **22** *from Open-Chain Amino-Acid Precursors* rac-**13**, -**14**, -**10n–p**, *and* -**11i–m**

Starting material	Products	R^3	R^1	R^2	R^4	*n*	Yield [%]	R_f values
rac-**11i**	**19i, 20i**	Me	Me	4-MeO-$C_6H_4CH_2$	Me_2N	1	37, 35	0.43, 0.32[a])
rac-**11k**	**19k, 20k**[b])	Me	Me	*t*-Bu	Me_2N	1	12, 11	0.36, 0.26[a])
rac-**11l**	**19l, 20l**	Me	Me	cyclo-Pr	Me_2N	1	31, 22	0.30, 0.24[a])
rac-**11m**	**19m, 20m**[b])	Me	Me	i-Pr	Me_2N	1	15, 11	[c])
rac-**10n**	**21n, 22n**	Ph	Me	Ph	Me_2N	2	27, 37	0.18, 0.10[d])
rac-**10o**	**21o, 22o**	Ph	CH_2=$CHCH_2$	Ph	Me_2N	2	41, 39	0.22, 0.16[d])
rac-**10p**	**19p, 20p**	Ph	Me	$PhCH_2$	$(CH_2)_4N$	1	40, 38	0.23, 0.16[d])
rac-**13**	**19q, 20q**	Me	H	i-Pr	Me_2N	1	41, 39	0.46, 0.33[a])
rac-**14**	**19r, 20r**	$PhCH_2$	H	$PhCH_2$	Me_2N	1	37, 36	0.27, 0.15[d])

[a]) SiO_2; Et_2O/i-PrOH 4:1.

[b]) 2-(4,4-Dialkyl-4,5-dihydro-2-methyl-5-oxoimidazol-1-yl)-*N*,*N*-dimethyl-3-phenylpropionamides were formed as side products (41% from *rac*-**11k** and 25% from *rac*-**11m**).

[c]) R_f Value not determined.

[d]) SiO_2; Et_2O/i-PrOH 98:2.

Table 2. *Synthesis of Dipeptides* **19** *and* **20** *and Tripeptides* **21** *and* **22** *from β-Tetralin-Derived Amino-Acid Precursors* rac-**11a–f**[a])

Starting material	Products	R^5	*n*	Isolated yield [%]	R_f Value (Et_2O/i-PrOH 92:8)
rac-**11a**	**21a, 22a**	H	2	49, 44	0.38, 0.31
rac-**11b**	**21b, 22b**	5-MeO	2	44, 43	0.38, 0.31
rac-**11c**	**21c, 22c**	6-MeO	2	43, 40.5	0.40, 0.29
rac-**11d**	**19d, 20d**	7-MeO	1	42, 44	0.49, 0.45
rac-**11d**	**21d, 22d**	7-MeO	2	43.5, 44	0.35, 0.28
rac-**11e**	**21e, 22e**	8-MeO	2	43.5, 45	0.40, 0.35
rac-**11f**	**21f, 22f**	6,7-$(MeO)_2$	2	41, 40.5	0.20, 0.15

[a]) $R^4 = (CH_2)_4N$.

Table 3. *Synthesis of Dipeptides* **19** *and* **20** *and Tripeptides* **21** *and* **22** *from α-Tetralin- and α-Indane-Derived Amino-Acid Precursors* rac-**11g–h**[a])

Starting material	Products	R^3	*n*	Isolated yield [%]	R_f Value (Et_2O/i-PrOH 92:8)
rac-**11g**	**19g, 20g**	Ph	1	47.5, 44	0.54, 0.49
rac-**11g**	**21g, 22g**	Ph	2	47.5, 45	0.51, 0.28
rac-**11g'**	**21g', 22g'**	4-Br-C_6H_4	2	41, 43.5	0.57, 0.36
rac-**11h**	**21h, 22h**	Ph	2	45, 46	0.44, 0.26

[a]) $R^4 = (CH_2)_4N$.

(*R*)- and (*S*)-**10**, which could either be isolated (*Method K*) or ring-opened *in situ* to give the N^2-acylated amino-acid methyl esters (*R*)- and (*S*)-**12** (*Methods M* and *N*) or the corresponding free acids (*R*)- and (*S*)-**11** (*Method L*; *Table 4*). In our experience, cleavage with CF_3SO_3H in anhydrous MeOH at 80° (*Method N*) consistently gave the best results, both in terms of product yield and percentage of chiral amine recovered (routinely between 70–80%).

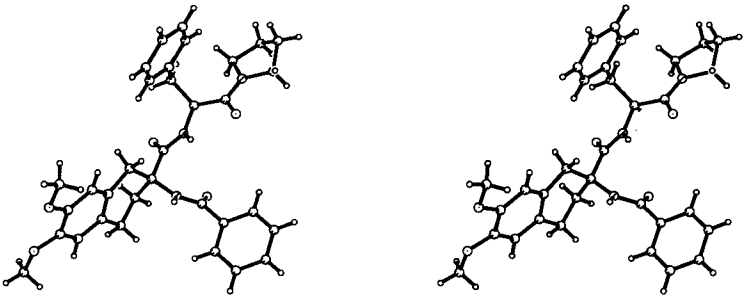


Fig. 1. *Stereoscopic drawing of* **20f** ((*S*,*S*)-configuration)

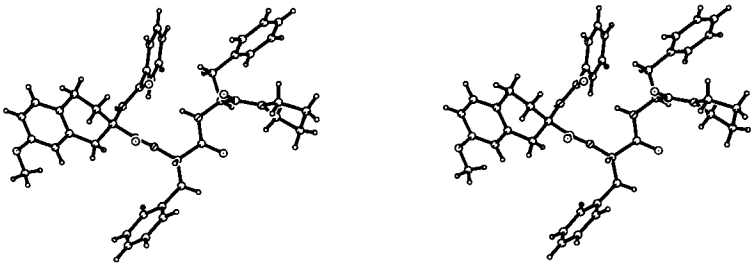


Fig. 2. *Stereoscopic drawing of* **22d** ((*S*,*S*,*S*)-configuration)

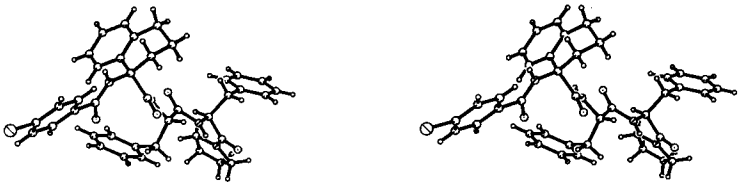


Fig. 3. *Stereoscopic drawing of* **21g′** ((*R*,*S*,*S*)-configuration)

Table 4. *Cleavage of Di- and Tripeptides* **19–22**

Diastereoisomers	Products	*Method*	$[\alpha]_D$ ($CHCl_3$)	Yield [%]
Acyclic series: **19i**, **20i**	(*R*)-**11i**, (*S*)-**11i**	*L*	− 60.4, + 58.4	85, 90
19k, **20k**	(*R*)-**12k**, (*S*)-**12k**	*M*	− 11.3, + 10.8	92, 92
19l, **20l**	(*R*)-**12l**, (*S*)-**12l**	*M*	Oil	95, 88
19m, **20m**	(*R*)-**11m**, (*S*)-**11m**	*L*	− 1.3[a]), [b])	91[b])
21n, **22n**	(*R*)-**11n**, (*S*)-**11n**	*L*	− 51, + 49	93, 92
21o, **22o**	(*R*)-**10o**, (*S*)-**10o**	*K*	− 87.3, + 83.7	94, 92
19p, **20p**	(*R*)-**10p**, (*S*)-**10p**	*K*	+ 86.1, − 71.2	89, 85
19q, **20q**	(*R*)-**13**, (*S*)-**13**	*O*	− 20.4, + 19.8	94, 91
19r, **20r**	(*R*)-**14**, (*S*)-**14**	*O*	+ 30.1, − 29.9	80, 78

Tab. 4 (cont.)

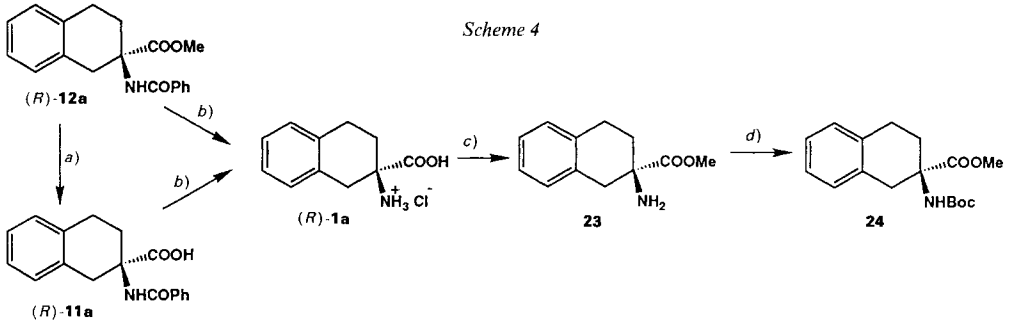
Diastereoisomers	Products	*Method*	$[\alpha]_D$ ($CHCl_3$)	Yield [%]
Cyclic series: **21a, 22a**	(*R*)-**12a**, (*S*)-**12a**	*N*	– 19.6, + 19.8[a])	98, 95
21b, 22b	(*R*)-**12b**, (*S*)-**12b**	*N*	– 28.5, + 26.5	96, 98
21c, 22c	(*R*)-**12c**, (*S*)-**12c**	*M*	– 68.0, + 67.7	92, 94
19d, 20d	(*R*)-**12d**, (*S*)-**12d**	*M*	– 118.3, + 116.5	96, 92
21e, 22e	(*R*)-**12e**, (*S*)-**12e**	*N*	– 142.5, + 138.5	93, 94
21f, 22f	(*R*)-**12f**, (*S*)-**12f**	*N*	– 90.0, + 92.0	93, 92
21g, 22g	(*R*)-**12g**, (*S*)-**12g**	*M*	– 71.0, + 69.3	92, 84
21h, 22h	(*R*)-**12h**, (*S*)-**12h**	*N*	– 156.3, + 156.7	95, 95

[a]) Optical rotation in MeOH. [b]) Data not recorded.

Purity of the resolved diastereoisomers **19–22** was checked by reversed-phase HPLC on an *RP-18-LiChrospher* (5 µm) column (UV detection) and also by careful examination of the 400-MHz ^{1}H-NMR spectra. As an additional control, the ^{1}H-NMR spectra (400 MHz, $CDCl_3$) of the chiral *N*-acylated amino-acid esters **12** in the presence of the chiral shift reagent (+)-(*S*)-1-(anthr-9-yl)-2,2,2-trifluoroethanol (TAE) were measured and compared to those of the racemic material under the same conditions. In all cases, optical purity was > 99%.

The conditions for the removal of the benzoyl group and subsequent protection of the chiral amino acid for incorporation into peptides as exemplified by the β-tetralin-derived amino acid (*R*)-**1a** (see *Scheme 4*) proved to be general. Thus, the benzoylated amino-acid

Scheme 4



a) LiOH·H_2O, THF/MeOH/H_2O 3:1:1, r.t. *b*) Aq. HCl soln. (37%), 100°. *c*) $SOCl_2$, 15% HCl in MeOH/MeOH 1:1. *d*) Di(*tert*-butyl) dicarbonate, DMF, r.t.

ester (*R*)-**12a** was treated with 37% aq. HCl solution at 100° for 24 h and the amino acid isolated either as the crude hydrochloride salt or by precipitation of the zwitter ion from H_2O at pH 7. Without further purification, the amino acid (*R*)-**1a** was esterified using modified *Fischer* conditions (see *Exper. Part*). The resulting amino-acid ester **23** was then reacted with di(*tert*-butyl) dicarbonate in DMF to provide the pure fully protected amino acid **24** in high yield after flash chromatography.

Discussion. – The method presented in this work for the resolution of α,α-disubstituted amino acids depends on the ability to separate the diastereoisomeric peptides **19**/**20**

and **21**/**22** on silica gel, and to selectively cleave the chiral auxiliaries **15**–**18** afterwards (*Scheme 3*). Previous experience had shown that selective cleavage was possible, due to the inherent propensities of α,α-disubstituted amino acids to readily form 1,3-oxazol-5(4*H*)-ones. In addition, mild reaction conditions had been found previously for the cleavage of the C-terminal dimethylamide group from standard mono-substituted amino acids without racemization [22].

The first chiral amines used were (*S*)-phenylalanine dimethylamide (**15**) and 1-[(*S*)-phenylalanyl]pyrrolidine (**16**; *Scheme 3*); attention was focused on secondary amides due to their increased stability towards hydrolysis. The chiral amines **15** and **16** were used to resolve the majority of the acyclic amino acids in this work. Two exceptions were 2-methyl-2-phenylglycine (*rac*-**1n**) and 2-allyl-2-phenylglycine (*rac*-**1o**) which were resolved with Phe-Phe-NMe_2 (**17**) because of the poor separation of the dipeptide diastereoisomers. Differences in R_f values on TLC plates (silica gel) for the diastereoisomers in *Table 1* ranged from 0.06 to 0.13 with mixtures i-PrOH/Et_2O. Yields varied from poor (**19k**/**20k**) to very good (**19q**/**20q** and **21o**/**22o**), depending on the nature of the compound and the reaction conditions. Poor yields were often due to the formation of imidazolidin-4-one side-products when N^2-acetyl protection (R^3=Me) was present[3]).

In the β-tetralin series (*Table 2*), preparation and separation of the diastereoisomers, obtained almost exclusively with chiral amine **18**, proceeded in high yield, using conditions that had been optimized on the early samples. In all cases, the benzoylated derivatives (R^3=Ph) were synthesized[3]). The better separation of diastereoisomeric tripeptides compared to the corresponding dipeptides is exemplified by the 7-methoxy-β-tetralin-derived amino acids (*Table 2*, **19d**/**20d** and **21d**/**22d**).

The best results in terms of separation were obtained for the α-tetralin- and α-indane-derived amino acids (*Table 3*). Differences in R_f values as large as 0.21 were observed, when Phe-Phe-$N(CH_2)_4$ (**18**) was used as the chiral amine. A possible explanation for this behavior might be the restricted movement of the back-bone around the α-position adjacent to the aromatic ring in the tetralin and indane unit, accentuating the differences in the conformation of the two diastereoisomers. It is also possible that electronic factors due to the proximity of the aromatic ring to the peptide chain might play a role.

The conditions for the selective amide cleavage (*Table 4*) were optimized primarily with respect to the yield of the amino-acid derivative in question and the ease and yield of recovery of the chiral resolving agent. For the resolution of standard amino acids (see **19q**/**20q** and **19r**/**20r**), the nature of the problem was somewhat different from that of the α,α-disubstituted amino acids, as only the latter readily formed 1,3-oxazol-5(4*H*)-ones under cleavage conditions. The best cleavage reagent for standard N^2-acylated mono-substituted amino acids was a 15% HBr solution in $MeNO_2$ (saturated with H_2O) at 80° (cleavage without racemization). For the α,α-disubstituted amino acids, using 3 equiv. of freshly distilled CF_3SO_3H in anh. MeOH at 80° gave both the highest yields of the N^2-acylated amino-acid esters (between 90 and 95%) and high recovery rates of the chiral amines (> 70%). The results were consistently better, than, *e.g.*, with 15% HCl(g) in MeOH. Other organic acids including CF_3COOH were tried instead of CF_3SO_3H. However, being weaker acids than CF_3SO_3H, these resulted in poor yields and long reaction times. Proceeding *via* the N^2-acyl-esters **12** rather than the N^2-acyl-acids **11** had the additional advantage of easy workup and purification using flash chromatography. Finally, isolation of the 1,3-oxazol-5(4*H*)-ones **10** in high yield after the cleavage required

strictly anhydrous conditions, and care had to be taken not to hydrolyze **10** upon acidic extraction of the chiral amine during workup.

Absolute configurations were assigned to the enantiomers of the α,α-disubstituted amino acids **1a–p** on the basis of the three new crystal structures for the di- or tripeptides **20f**, **22d**, and **21g'** (*Figs. 1–3*), and one obtained previously [23]. In each of these cases, it was the least polar of the two diastereoisomeric di- or tripeptide (*i.e.* **19** or **21**) that contained the amino acid of (*R*)-configuration. At present, it is difficult to offer a rationale for this behavior without additional data from solution studies.

Conclusion. – In this study, we have developed an efficient and general method for the preparation of optically pure α,α-disubstituted amino acids, with very little restriction on the nature of their side chains. Multi-gram quantities of both enantiomers are routinely prepared in our laboratories using the standard conditions and procedures outlined above. The chiral resolving agents used are readily synthesized from (*S*)-phenylalanine and can be recovered in good yield. Furthermore, new and simpler chiral auxiliaries were recently prepared giving improved separation [24].

This efficient separation method should stimulate the design and synthesis of new and interesting chiral α,α-disubstituted amino acids, which are anticipated to exhibit interesting conformational properties, particularly when incorporated into peptides.

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Experimental Part

General. All reactions with air- or moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified by distillation shortly before use. THF was distilled under Ar from Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2, and DMF over ninhydrin and kept over 4-Å molecular sieves. All other reactants were 'reagent-grade' unless described otherwise. Anal. TLC: 2.5 × 10 cm precoated TLC plates, SiO_2 *60F-254*, layer thickness 0.25 mm (*E. Merck & Co.*, Darmstadt, Germany). Flash chromatography (FC): *E. Merck* SiO_2 *60* (230–400 mesh ASTM); according to [15]. M.p.: *Büchi-SMP-20* apparatus; uncorrected. IR Spectra: *Nicolet-7199-FT* spectrophotometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; in $CDCl_3$; TMS as internal standard; chemical shifts of signal centres and ranges in ppm (δ), *J* in Hz; TAE = (+)-(*S*)-1-(anthr-9-yl)-2,2,2-trifluoroethanol.

General Methods. – *Method A.* A mixture of ketone **2a–f,i–l** (50 mmol), KCN 4.88 g, 75.0 mmol) and $(NH_4)_2CO_3$ (28.5 g, 0.25 mol) was placed in a 500-ml steel autoclave. To this mixture was added EtOH/H_2O (4:1 for **2b–f,i–l**; 1:1 for **2a**; 200 ml), the resulting suspension stirred under N_2 for 18 h 80° and the mixture cooled to r.t. and poured into ice (100 g) and H_2O (400 ml). The suspension was stirred for 2 h at r.t. and filtered, and the residue washed with H_2O (500 ml). The remaining solid was dried (P_2O_5) in a desiccator overnight and a sample recrystallized from EtOH/H_2O yielding hydantoin *rac*-**3a–f,i–l** as greyish powder.

Method B. Ketones **2g–h** (50.0 mmol) were treated following *Method A* for 36 h at 120°: *rac*-**3g,h**.

Method C. To a mixture of hydantoin *rac*-**3a–l** (50.0 mmol) and $Ba(OH)_2 \cdot 8\ H_2O$ (78.9 g, 5 equiv.) was added H_2O to a total volume of 200 ml in a 500-ml steel autoclave. The mixture was stirred for 24 h at 125°, cooled to r.t., and slowly acidified under vigorous stirring with 4N aq. H_2SO_4 (200 ml). The suspension was stirred on a steam bath for 1 h, cooled to r.t., and filtered and the precipitate ($BaSO_4$) washed with H_2O (200 ml). The aq. soln. was evaporated to *ca.* 200 ml and neutralized with conc. aq. NH_3 soln. The amino acid *rac*-**1a–l** was allowed to crystallize overnight, filtered, washed with H_2O (50 ml), and dried in a desiccator (P_2O_5) under reduced pressure.

Method D. To a mechanically, vigorously stirred soln. (or suspension) of amino acid *rac*-**1a–h** (50.0 mmol) in 2N aq. NaOH (30 ml) were simultaneously added (2 funnels or 2 syringes) under ice-bath cooling 6N aq. NaOH (18.3 ml) and the corresponding benzoyl chloride (R^3COCl; 125 mmol), so that the temp. in the mixture did not exceed 10°. The mixture was then allowed to come to r.t. under vigorous stirring, the latter being essential for reproducible yields, stirred for 2 h at r.t., and poured on ice (50 g), 2N aq. HCl (100 ml) and AcOEt (200 ml). The aq. layer was extracted with AcOEt (2 × 100 ml), and the combined org. phase washed with brine (300 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH/dioxane 2:1 (150 ml), followed by addition of 3N aq. NaOH (100 ml) under ice-bath cooling. The mixture was then stirred over night at r.t., carefully acidified with conc. aq. HCl soln., and extracted with $CHCl_3$ (3 × 200 ml) and AcOEt (200 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue dried under reduced pressure and suspended in Et_2O (200 ml). The suspension was stirred for 2 h at r.t. and filtered, the residue washed with Et_2O/hexane 1:1 (2 × 50 ml), and the solid *rac*-**11a–h** (R^3 = Ph) or *rac*-**11g′** (R^3 = 4-BrC_6H_4) dried in a desiccator (P_2O_5) under reduced pressure (the filtrate contained mainly benzoic acid and only small amounts of the N^2-benzoylated amino acid).

Method E. A mixture of amino acid *rac*-**1i–l**, (10.0 mmol), pyridine (10 ml), and Ac_2O (10 ml) was stirred for 15 h at r.t. and 1 h at reflux. The mixture was cooled, poured onto ice (20 g) and H_2O (20 ml), and stirred for 3 h, the white precipitate filtered, and the filtrate evaporated and again mixed with H_2O (10 ml) and stirred. The precipitates were combined and dried under reduced pressure to yield the pure N^2-acetylated amino acid *rac*-**11i–l** (R^3 = Me) as white powder.

Method F. To a stirred soln. of **6** or **7** (10.0 mmol) in CH_2Cl_2 (30 ml) was added under Ar at r.t. DCC (2.1 g) in small portions. The mixture was stirred for 2 h at r.t. and filtered, the residue washed with CH_2Cl_2 (2 × 5 ml), the filtrate evaporated, and the residue **8** or **9**, resp., dried under reduced pressure for 1 h. To the residue was added DMF (40 ml), $(i\text{-}Pr)_2EtN$ (10.0 mmol), and R^2X (15–20 mmol). The mixture was stirred for 8–12 h at 80° and then evaporated and the residue chromatographed (SiO_2 (150 g), Et_2O/hexane as indicated): *rac*-**10n–p** (R^3 = Ph) as colorless oils, which solidified upon drying under reduced pressure.

Method G. To a suspension of *rac*-**11i–m** (10.0 mmol) in CH_2Cl_2 or THF (10–20 ml) was added under Ar *N,N′*-carbonyldiimidazole (CDI; 10.5 mmol) at r.t. The mixture was stirred until no more CO_2 evolved (*ca.* ½–1 h), followed by addition of **15** (10.0 mmol). The mixture was stirred for an additional 15–72 h (as indicated) and then poured onto ice (20 g), 2N aq. HCl (10 ml), and CH_2Cl_2 (30 ml). The org. layer was extracted with sat. aq. $NaHCO_3$ soln. (30 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (500 g), Et_2O/i-PrOH as indicated): pure epimeric dipeptides **19**/**20i–m** as white solids, which were further purified by recrystallization (where possible).

Method H. To a stirred suspension of N^2-benzoylated amino acid *rac*-**11a–g, g′** (50.0 mmol) in CH_2Cl_2 (200 ml) was added DCC (10.83 g, 1.05 equiv.) in portions of 1 g. The resulting suspension was vigorously stirred for 3 h at r.t., filtered, and washed with CH_2Cl_2 (100 ml). The solvent was evaporated, the residue dried under reduced pressure, and dissolved in DMF (150 ml), and **16** or **18** added (65.0 mmol). The mixture was stirred for 24 h at 50°, cooled to r.t., and poured onto 2N aq. HCl (150 ml), ice (100 g), and AcOEt (300 ml). The aq. layer was extracted with AcOEt (200 ml), the combined org. fraction washed with H_2O (2 × 200 ml) and brine (200 ml), dried ($MgSO_4$), and evaporated, and the residue dried under reduced pressure. The diastereoisomeric peptides **19**/**20d,g** or **21**/**22a–g, g′** were separated and purified as indicated. Amorphous solids were suspended in hexane with stirring for 1 h, filtered, washed with hexane, and dried under reduced pressure overnight.

Method I. A stirred suspension of N^2-benzoylated amino acid *rac*-**11h** (50.0 mmol) in Ac_2O (50 ml) was heated at 70° for 1.5 h, cooled to r.t., and evaporated. The residue was dried (P_2O_5) in a desiccator under reduced pressure over night. The crude 1,3-oxazol-5(4*H*)-one was dissolved in DMF (150 ml) and proceeded as described in *Method H*: **21**/**22h**.

Method K. Through a stirred suspension of amide **19**/**20p** or **21**/**22o** (10.0 mmol) in dry toluene (30 ml), kept at 80°, was passed a steady stream of dry HCl gas for 2–3 min. The mixture was stirred for an additional 30 min, cooled to r.t., and evaporated and the residue dried under reduced pressure for 30 min. The residue was suspended in Et_2O (30 ml), stirred for 30 min and filtered and the filtrate evaporated. The residue was chromatographed on SiO_2 and purified as indicated: **10o, p**.

Method L. A mixture of amides **19**/**20i**, **19**/**20m**, or **21**/**22n** (10.0 mmol) and 4N aq. HCl/dioxane 1:1 (30 ml) was stirred for 1–4 h at 80° (TLC monitoring), cooled to r.t., and poured onto $CHCl_3$ (80 ml) and H_2O (50 ml). The aq. layer was extracted with $CHCl_3$ (2 × 50 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified as indicated: **11i, m, n**.

Method M. A stirred soln. of peptide **19**/**20d, k, l** or **21**/**22c, g** (50.0 mmol) in freshly prepared 15% HCl/MeOH (150 ml) was heated in a pyrolysis tube for 6–8 h, cooled to r.t., and evaporated. The residue was extracted with 2N aq. HCl (100 ml) and AcOEt/Et_2O 1:1 (200 ml). The org. phase was washed with brine (100 ml), dried ($MgSO_4$),

and evaporated. The residue was chromatographed on SiO_2 (800 g) with AcOEt/hexane 2:3 to yield the amino-acid methyl ester **12c, d, g, k, l** as amorphous solid. The aq. phase was brought to pH *ca.* 10 by addition of 3N aq. NaOH and extracted with $CHCl_3$ (3 × 150 ml). The combined org. fractions were dried ($MgSO_4$) and evaporated. From the residue, **15** or **16** were recovered as the trifluoroacetate by addition of Et_2O and CF_3COOH, and **17** or **18** were obtained in 60–70% yield by crystallization from Et_2O.

Method N. To a stirred soln. of peptide **21/22a, b, e, f, h** (50.0 mmol) in freshly distilled MeOH (150 ml) was added under Ar CF_3SO_3H (*Fluka*; 13.2 ml, 3 quiv.) at 0°. The mixture was then heated for 20 h at 80°, cooled to r.t., and evaporated. The residue was mixed with 2N aq. HCl (150 ml), ice (100 g), and AcOEt (200 ml), the org. phase extracted with brine (200 ml), dried ($MgSO_4$), and evaporated, and the product purified as described in *Method M*: **12a, b, e, f, h**.

Method O. A mixture of $MeNO_2$ (100 ml) and H_2O (100 ml) was shaken in a separating funnel for *ca.* 2 min. The layers were separated, and the $MeNO_2$ phase was saturated under ice-bath cooling with dry HBr gas: *ca.* 16% HBr soln. in $MeNO_2$ (sat. with H_2O). A mixture of amide **19/20q, r** (10.0 mmol) and 16% HBr/$MeNO_2$ soln. (30 ml) was heated for 1–2 h at 60–70°, cooled to r.t., and poured onto ice (20 g), H_2O (20 ml), and $CHCl_3$ (70 ml). The aq. layer was extracted with $CHCl_3$ (2 × 50 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified as indicated: **13** (= **11q**), **14** (= **11r**).

Method P. To a stirred soln. of N^2-benzoylated amino acid *rac*-**11a–h** (10.0 mmol) in DMF (30 ml) was added under Ar DBU (1.79 ml, 1.2 equiv.) and MeI (0.94 ml, 1.5 equiv.) at 0°. The mixture was stirred for 6 h at r.t., poured on ice (15 g), 2N aq. HCl (50 ml), and AcOEt (80 ml), the aq. phase extracted with AcOEt (2 × 50 ml), the combined org. phase washed with H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated, and the residue crystallized from AcOEt/hexane 1:2: methyl ester *rac*-**12a–h** as white solid.

Compounds 1, 3, 10–13, and 19–22. – rac-*3′,4′-Dihydrospiro[imidazolidine-4,2′(1′H)-naphthalene]-2,5-dione* (*rac*-**3a**)[5]. From 3,4-dihydronaphthalen-2(1*H*)-one (= *β*-tetralone; **2a**; *Fluka*; 15.0 g, 103 mmol) in EtOH/H_2O 1:1 according to *Method A*: 20.2 g (90.7%) of *rac*-**3a**. M.p. 268.2°. IR (KBr): 3438*w*, 3177*m*, 3063*m*, 2937*w*, 2765*w*, 1775*s*, 1735*s*, 1496*w*, 1450*w*, 1410*m*, 1302*w*, 1223*w*, 1051*w*, 791*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.71 (br. *s*, 1 NH); 8.32 (br. *s*, 1 NH); 7.1 (*m*, 4 arom. H); 3.12, 2.77 (2*d*, *J* = 17.5, 2 aliph. H); 2.9 (*m*, 2 aliph. H); 2.05–1.7 (*m*, 2 aliph. H). MS: 216 (52, M^+), 201 (11), 199 (22), 130 (20), 104 (100), 103 (17), 78 (13). Anal. calc. for $C_{12}H_{12}N_2O_2$ (216.24): C 66.65, H 5.59, N 12.96; found: C 66.43, H 5.53, N 12.89.

rac-*3′,4′-Dihydro-5′-methoxyspiro[imidazolidine-4,2′(1′H)-naphthalene]-2,5-dione* [7c] (*rac*-**3b**). From 3,4-dihydro-5-methoxynaphthalen-2(1*H*)-one (**2b**; 20.0 g, 113.5 mmol) [20] according to *Method A*: 25.2 g (90.2%) of *rac*-**3b**. M.p. 270–272° (dec.). IR (KBr): 3476*w*, 3420*w*, 3304*m*, 3205*m*, 2940*w*, 1770*s*, 1733*s*, 1715*s*, 1586*w*, 1470*m*, 1405*w*, 1261*m*, 1047*w*, 777*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.69 (br. *s*, 1 NH); 8.28 (br. *s*, 1 NH); 7.13 (*t*, *J* = 9.1, 1 arom. H); 6.77, 6.68 (2*d*, *J* = 9.1, 2 arom. H); 3.77 (*s*, MeO); 3.15–3.0, 2.95–2.55, 2.0–1.75 (3*m*, 6 aliph. H). MS: 246 (60, M^+), 231 (29), 160 (22), 134 (100), 104 (60), 91 (26). Anal. calc. for $C_{13}H_{14}N_2O_2$ (246.27): C 63.40, H 5.73, N 11.38; found: C 63.05, H 5.75, N 11.24.

rac-*3′,4′-Dihydro-6′-methoxyspiro[imidazolidine-4,2′(1′H)-naphthalene]-2,5-dione* [7c] (*rac*-**3c**). From 3,4-dihydro-6-methoxynaphthalen-2(1*H*)-one (**2c**; *Aldrich*; 10.0 g, 56.75 mmol) according to *Method A*: 11.46 g (82.0%) of *rac*-**3c**. M.p. 292°. IR (KBr): 3238*m*, 3170*m*, 3060*m*, 2933*w*, 2836*w*, 1774*s*, 1732*s*, 1612*m*, 1503*m*, 1407*m*, 1297*m*, 1270*m*, 1035*w*, 796*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.69 (br. *s*, 1 NH); 8.29 (br. *s*, 1 NH); 7.05–6.95, 6.75–6.65 (2*m*, 3 arom. H); 3.71 (*s*, MeOH); 3.05, 2.69 (2*d*, *J* = 17.3, 2 aliph. H); 2.95–2.75, 2.0–1.7 (2*m*, 4 aliph. H). MS: 246 (29, M^+), 134 (100), 91 (10).

rac-*3′,4′-Dihydro-7′-methoxyspiro[imidazolidine-4,2′(1′H)-naphthalene]-2,5-dione* [7c] (*rac*-**3d**). From 3,4-dihydro-7-methoxynaphthalen-2(1*H*)-one (**2d**; *Aldrich*; 25.0 g, 137.6 mmol) according to *Method A*: 28.1 g (83.0%) of *rac*-**3d**. Recrystallization from $CHCl_3$/MeOH 1:1 yielded 26.1 g (77.0%) of *rac*-**3d**. White powder. M.p. > 250° (dec.). IR (KBr): 3223*m*, 3170*m*, 3061*m*, 2839*w*, 2767*w*, 1773*s*, 1735*s*, 1614*w*, 1503*m*, 1409*m*, 1269*m*, 1053*m*, 810*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.72 (br. *s*, 1 NH); 8.30 (br. *s*, 1 NH); 7.1–7.0, 6.75–6.6 (2*m*, 3 arom. H); 3.70 (*s*, MeO); 3.09, 2.73 (2*d*, *J* = 17.2, 2 aliph. H); 2.9–2.7, 2.0–1.7 (2*m*, 4 aliph. H). MS: 246 (88, M^+), 160 (18), 134 (100), 91 (19). Anal. calc. for $C_{13}H_{14}N_2O_2$ (246.27): C 63.40, H 5.73, N 11.38; found: C 63.40, H 6.02, N 11.40.

rac-*3′,4′-Dihydro-8′-methoxyspiro[imidazolidine-4,2′(1′H)-naphthalene]-2,5-dione* [25] (*rac*-**3e**). From 3,4-dihydro-8-methoxynaphthalen-2(1*H*)-one (**2e**; 20.0 g, 113.5 mmol) [21] according to *Method A*: 24.2 g (86.6%) of *rac*-**3e**. M.p. 211–212°. IR (KBr): 3192*w* (br.), 3065*w*, 2936*w*, 2836*w*, 1774*s*, 1727*s*, 1586*w*, 1470*m*, 1440*w*, 1405*m*, 1344*w*, 1293*w*, 1255*m*, 1096*w*, 1046*w*, 797*w*, 765*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.71 (br. *s*, 1 NH); 8.30 (br. *s*, 1 NH); 7.2–7.05 (*m*, 1 arom. H); 6.85–6.7 (*m*, 2 arom. H); 3.75 (*s*, MeO); 2.95–2.8 (*m*, 2 aliph. H); 2.86, 2.68 (2*d*, *J* = 17.5, 2 aliph. H); 2.0–1.7 (*m*, 2 aliph. H). MS: 246 (40, M^+), 134 (100), 104 (44), 91 (17).

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[5]) Compound *rac*-**3a** is now commercially available from *Aldrich*.

rac-*3',4'-Dihydro-6',7'-dimethoxyspiro[imidazolidine-4,2'(1'H)-naphthalene]-2,5-dione* [7c] (*rac*-**3f**). From 3,4-dihydro-6,7-dimethoxynaphthalen-2(1*H*)-one (**2f**; *Aldrich*; 10.0 g, 48.5 mmol) according to *Method A*. Recrystallization from EtOH/H_2O gave 11.28 g (84.9%) of *rac*-**3f**. M.p. 285–287°. IR (KBr): 3322*m*, 3163*w*, 3058*w*, 2937*w*, 1771*s*, 1707*s*, 1612*w*, 1518*s*, 1410*m*, 1351*m*, 1261*m*, 1227*m*, 1117*m*, 1014*w*, 648*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.67 (br. *s*, 1 NH); 8.27 (br. *s*, 1 NH); 6.69, 6.66 (2*s*, 2 arom. H); 3.71, 3.69 (2*s*, 2 MeO); 3.03, 2.66 (2*d*, *J* = 16.7, 2 aliph. H); 2.9–2.7, 2.0–1.7 (2*m*, 4 aliph. H). MS: 276 (59, M^+), 164 (100), 149 (12), 121 (20), 103 (12), 91 (12), 77 (12). Anal. calc. for $C_{14}H_{16}N_2O_4$ (276.29): C 60.86, H 5.84, N 10.14; found: C 60.65, H 5.87, N 10.07.

rac-*3',4'-Dihydrospiro[imidazolidine-4,1'(2'H)-naphthalene]-2,5-dione* [17] (*rac*-**3g**). From 3,4-dihydronaphthalen-1(2*H*)-one (= α-tetralone; **2g**; *Fluka*; 4.5 g, 30.8 mmol) according to *Method B*: 4.32 g (96.3%) of *rac*-**3g**. M.p. 244°. IR (KBr): 3219*m* (br.), 3048*w*, 2943*w*, 1767*m*, 1707*s*, 1429*m*, 1225*w*, 1027*w*, 744*m*, 636*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.83 (br. *s*, 1 NH); 8.52 (br. *s*, 1 NH); 7.3–7.0 (*m*, 4 arom. H); 2.85–2.7 (*m*, 2 aliph. H); 2.2–1.7 (2*m*, 4 aliph. H). MS: 216 (57, M^+), 188 (13), 187 (25), 172 (8), 160 (9), 145 (57), 128 (29), 117 (100), 104 (40).

rac-*2',3'-Dihydro-6'-methoxyspiro[imidazolidine-4,1'(1'H)-indene]-2,5-dione* [17] (*rac*-**3h**). From 2,3-dihydro-6-methoxy-1*H*-inden-1-one (**2h**; *Fluka*; 10.0 g, 61.7 mmol) according to *Method B*. Recrystallization from EtOH/H_2O 1:1 gave 11.6 g (81%) of *rac*-**3h**. M.p. 186–190°. IR (KBr): 3392*w* (br.), 3253*m* (br.), 3056*w*, 1772*s*, 1731*s*, 1611*w*, 1496*m*, 1437*m*, 1287*m*, 1214*m*, 1023*m*, 767*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.73 (br. *s*, 1 NH); 8.40 (br. *s*, 1 NH); 7.25–7.15 (*m*, 1 arom. H); 6.95–6.85 (*m*, 1 arom. H); 6.7–6.65 (*m*, 1 arom. H); 3.73 (*s*, MeO); 3.05–2.85 (*m*, 2 aliph. H); 2.6–2.45 (*m*, 1 aliph. H); 2.25–2.1 (*m*, 1 aliph. H). MS: 232 (100, M^+), 204 (16), 173 (24), 161 (88), 160 (95), 146 (25), 121 (21), 117 (19), 77 (20). Anal. calc. for $C_{12}H_{12}N_2O_3$ (232.24): C 62.06, H 5.21, N 12.06; found: C 62.02, H 5.23, N 12.05.

rac-*5-(4-Methoxybenzyl)-5-methylimidazolidine-2,4-dione* [26] (*rac*-**3i**). From 4-methoxybenzyl methyl ketone (**2i**; *Fluka*, 5.0 g, 30 mmol) and KCN (4.0 g, 60 mmol) according to *Method A*: 6.5 g (93%) of *rac*-**3i**. M.p. 193°. IR (KBr): 3340*m*, 3220*m*, 3075*w*, 2940*w*, 1725*s*, 1715*s*, 1615*w*, 1515*m*, 1400*m*, 1305*w*, 1285*m*, 1255*m*, 1180*m*, 1040*w*, 760*m*, 665*w*. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 7.77 (br. *s*, 1 NH); 7.2–6.7 (*m*, *AA'BB'*, J_{AB} = 7.0, 4 arom. H); 3.68 (*s*, MeO); 2.78, 2.54 (2*d*, *AB*, J_{AB} = 14.0, MeOC$_6$H$_4$C*H*$_2$); 1.27 (*s*, Me–C(5)). ^{13}C-NMR ((D$_6$)DMSO, 100 MHz): 178.3 (*s*, C(4)); 158.1 (*s*, C(2)); 156.5, 131.1, 127.4, 113.4 (6 arom. C); 63.4 (*s*, C(5)); 55.0 (*q*, MeO); 42.2 (*t*, 4-MeOC$_6$H$_4$*C*H$_2$); 24.1 (*q*, *Me*–C(5)). MS: 234 (5, M^+), 121 (100), 91 (12), 78 (14), 77 (19), 65 (8), 51 (15), 42 (31). Anal. calc. for $C_{12}H_{14}N_2O_3$ (234.26): C 61.53, H 6.02, N 11.96; found: C 61.43, 5.87, N 11.76.

rac-*5-(tert-Butyl)-5-methylimidazolidine-2,4-dione* [31] (*rac*-**3k**). From *tert*-butyl methyl ketone (= pinacoline; **2k**; *Fluka*; 3.0 g, 30 mmol) and KCN (4.0 g, 60 mmol) according to *Method A*: 4.44 g (87%) of *rac*-**3k**. M.p. 218–219°. IR (KBr): 3240*m*, 3100*m*, 3050*m*, 2960*m*, 1760*m*, 1730*s*, 1430*m*, 1370*w*, 1270*w*, 1220*w*, 1010*w*, 775*m*. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 10.40, 7.87 (2 br. *s*, 2 NH); 1.2 (*s*, Me–C(5)); 0.9 (*s*, *t*-Bu). MS: 170 (< 1, M^+), 155 (2), 114 (100), 83 (41), 57 (64), 42 (84), 41 (96). Anal. calc. for $C_8H_{14}N_2O_3$ (170.22): C 56.45, H 8.29, N 16.46; found: C 56.71, 8.04, N 16.62.

rac-*5-Cyclopropyl-5-methylimidazolidine-2,4-dione* [31] (*rac*-**3l**) [26]. From cyclopropyl methyl ketone (**2l**; *Fluka*; 8.98 g, 100 mmol) and KCN (13.9 g, 210 mmol) according to *Method A*: 13.1 g (77%) of *rac*-**3l**. M.p. 145–145.2° ([27]: 147–148°). IR (KBr): 3440*m*, 2990*m*, 1775*m*, 1720*s*, 1400*m*, 1260*m*, 1025*m*, 910*w*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.73 (br. *s*, 2 NH); 1.33 (*s*, Me–C(5)); 1.15–0.95 ('*t*', (CH$_2$)$_2$C*H*); 0.5–0.15 (*m*, (C*H*$_2$)$_2$CH). MS: 154 (< 1, M^+), 139 (20), 126 (48), 113 (75), 83 (42), 68 (53), 42 (100). Anal. calc. for $C_7H_{10}N_2O_2$ (154.17): C 54.20, H 6.54, N 18.17; found: C 54.38, H 6.59, N 17.99.

rac-*2-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid* (*rac*-**1a**) [28]. From **3a** (18 g, 83.0 mmol) according to *Method C*: 14.25 g (89.8%) of *rac*-**1a**. M.p. > 230° (dec.). IR (KBr): 3343*m* (br.), 3216*m* (br.), 3017*m* (br.), 2928*m* (br.), 1696*m*, 1638*s*, 1551*s*, 1496*m*, 1448*m*, 1404*s*, 1305*m*, 1073*w*, 794*w*, 748*m*, 544*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.62 (br. *s*, 3 NH); 7.15–7.0 (*m*, 4 arom. H); 3.31 (*d*, *J* = 17.5, 2 aliph. H); 2.9–2.65 (*m*, 3 aliph. H); 2.15–2.0, 1.9–1.75 (2*m*, 2 aliph. H). MS: 191 (19, M^+), 174 (18), 146 (100), 129 (88), 104 (63).

Enantiomer (*R*)-**1a**. To (*R*)-**11a** (1 g, 3.39 mmol) in a pyrolysis tube was added 37% aq. HCl soln. (10 ml). The resulting suspension was heated at 100° for 5 h and the mixture then diluted with H_2O (50 ml) and extracted with Et_2O (3 × 50 ml). The aq. phase was evaporated and the white solid dried in a desiccator overnight over P_2O_5 under high vacuum: 752 mg (97.4%) of (*R*)-**1a**, which was used directly without further purification.

rac-*2-Amino-1,2,3,4-tetrahydro-5-methoxynaphthalene-2-carboxyclic Acid* [7c] (*rac*-**1b**). From **3b** (30.0 g, 121.8 mmol) according to *Method C*: 23.9 g (88.7%) of *rac*-**1b**. M.p. > 254° (dec.). IR (KBr): 3430*w* (br.), 3039*m*, 2936*m*, 2654*w* (br.), 1631*s*, 1586*s*, 1517*m*, 1469*s*, 1387*s*, 1524*s*, 1083*m*, 769*m*. ^{1}H-NMR (D$_2$O, 250 MHz): 7.15–7.05, 6.8–6.7 (2*m*, 3 arom. H); 3.72 (*s*, MeO); 3.07, 2.57 (2*d*, *J* = 16.9, 2 aliph. H); 2.65–2.5, 2.0–1.85, 1.8–1.65 (3*m*,

4 aliph. H). MS: 221 (24, $M^{+\cdot}$), 204 (21), 176 (74), 159 (100), 144 (44), 134 (35), 115 (33), 104 (45), 91 (37), 77 (21), 65 (22).

rac-*2-Amino-1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylic Acid* [7c] (*rac*-**1c**). From **3c** (10.0 g, 40.6 mmol) according to *Method C*: 7.63 g (85%) of *rac*-**1c**. IR (KBr): 3344*m*, 3214*m*, 3008*m*, 2960*m*, 1695*w*, 1636*s*, 1610*s*, 1550*s*, 1506*s*, 1448*m*, 1403*m*, 1296*m*, 1240*s*, 1072*w*, 809*w*. ^{1}H-NMR (D_2O, 250 MHz): 7.60 (br. *s*, *ca.* 3 NH); 7.0–6.95, 6.75–6.65 (2*m*, 3 arom. H); 3.70 (*s*, MeO); 3.23, 2.65 (2*d*, J = 17.7, 2 aliph. H); 2.85–2.65, 2.15–2.0, 1.9–1.75 (3*m*, 4 aliph. H). MS: 221 (16, $M^{+\cdot}$), 204 (52), 176 (46), 159 (46), 134 (100), 115 (12), 104 (13), 88 (15), 65 (10).

rac-*2-Amino-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-carboxylic Acid* [7c] (*rac*-**1d**). From **3d** (25.0 g, 101.5 mmol) according to *Method C*: 20.66 g (92%) of *rac*-**1d**. M.p. > 290°. IR (KBr): 3426*w* (br.), 3000*m*, 2930*m*, 2837*m*, 2675*w*, 2601*w*, 1612*s*, 1554*s*, 1504*s*, 1449*m*, 1393*s*, 1299*m*, 1262*m*, 1158*w*, 1033*w*, 813*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.60 (br. *s*, *ca.* 3 NH); 7.05–6.95, 6.75–6.6 (2*m*, 3 arom. H); 3.70 (*s*, MeO); 3.30, 2.66 (2*d*, J = 17.3, 2 aliph. H); 2.8–2.55, 2.1–1.95, 1.85–1.7 (3*m*, 4 aliph. H). MS: 221 (24, $M^{+\cdot}$), 204 (37), 176 (33), 159 (100), 144 (21), 134 (50), 88 (18).

rac-*2-Amino-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-carboxylic Acid* [27] (*rac*-**1e**) [25]. From **3e** (15.0 g, 60.9 mmol) according to *Method C*: 11.5 g (85%) of *rac*-**1e**. M.p. 259–261°. IR (KBr): 3432*w* (br.), 3003*m*, 2947*m*, 2835*m*, 2674*w*, 2595*w*, 1720*w*, 1617*s*, 1586*s*, 1533*m*, 1470*s*, 1400*m*, 1333*w*, 1255*s*, 1099*m*, 760*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.1–7.0 (*m*, 1 arom. H); 6.75–6.6 (*m*, 2 arom. H); 3.67 (*s*, MeO); 3.10, 2.70 (2*d*, J = 17.5, 2 aliph. H); 2.8–2.65 (*m*, 2 aliph. H); 2.15–1.85 (*m*, 2 aliph. H). MS: 221 (22, $M^{+\cdot}$), 204 (25), 176 (100), 159 (60), 144 (30), 134 (40), 104 (48), 91 (24).

rac-2-Amino-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carboxyclic Acid [7c] (*rac*-**1f**). From **3f** (10.0 g, 36.2 mmol) according to *Method C*: 7.57 g (83.2%) of *rac*-**1f**. M.p. > 300°. IR (KBr): 3495*w* (br.), 3390*w* (br.), 3242*w* (br.), 3000*m*, 2965*m*, 2837*m*, 2643*w*, 2559*w*, 1640*s*, 1612*s*, 1572*s*, 1515*s*, 1464*m*, 1397*m*, 1301*m*, 1252*s*, 1226*m*, 1119*s*, 1008*w*, 863*w*. ^{1}H-NMR (D_2O, 250 MHz): 6.87, 6.84 (2*s*, 2 arom. H); 3.64, 3.63 (2*s*, 2 MeO); 3.35, 2.92 (2*d*, J = 17.7, 2 aliph. H); 3.05–2.65, 2.4–2.25, 2.2–2.05 (3*m*, 4 aliph. H). MS: 251 (49, $M^{+\cdot}$), 234 (57), 206 (34), 189 (63), 175 (19), 164 (100), 149 (27), 121 (14), 73 (15).

rac-*1-Amino-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid* [29] (*rac*-**1g**). From **3g** (20.0 g, 92.5 mmol) according to *Method C*: 16.81 g (95%) of *rac*-**1g**. M.p. 244–245° (dec.). IR (KBr): 3441*m* (br.), 3096*m* (br.), 2941*m* (br.), 1626*s*, 1581*s*, 1536*s*, 1448*w*, 1378*s*, 1292*w*, 738*m*, 574*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.92 (br. *s*, 3 NH); 7.45–7.35 (*m*, 1 arom. H); 7.25–7.05 (*m*, 3 arom. H); 2.8–2.65 (*m*, 2 aliph. H); 2.4–2.2 (*m*, 1 aliph. H); 2.10–1.65 (*m*, 3 aliph. H). MS: 174 (1, $[M - NH_3]^+$), 146 (100, $[M - COOH]^+$), 129 (25).

rac-*1-Amino-2,3-dihydro-6-methoxy-1*H*-indene-1-carboxylic Acid* (*rac*-**1h**). From **3h** (10 g, 43.1 mmol) according to *Method C*: 8.03 g (90%) of *rac*-**1h**. M.p. 220–222° (dec.). IR (KBr): 3542*w* (br.), 3064*m* (br.), 2942*m*, 1673*m*, 1610*s*, 1576*s*, 1520*m*, 1492*s*, 1453*w*, 1295*m*, 1281*m*, 1154*w*, 1028*m*, 866*w*, 823*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.5–7.5 (br. *s*, 3 NH); 7.2–7.1 (*m*, 1 arom. H); 7.05–6.95 (*m*, 1 arom. H); 6.85–6.75 (*m*, 1 arom. H); 3.70 (*s*, MeO); 3.05–2.8 (*m*, 2 aliph. H); 2.75–2.6 (*m*, 1 aliph. H); 2.05–1.9 (*m*, 1 aliph. H). MS: 207 (< 1, $M^{+\cdot}$), 163 (14), 162 (100), 147 (11), 119 (12). Anal. calc. for $C_{11}H_{13}NO_3$ (207.33): C 63.76, H 6.32, N 6.75; found: C 63.55, H 6.26, N 6.58.

rac-*2,O^4-Dimethyltyrosine* [26] (= rac-*2-Amino-3-(4-methoxyphenyl)-2-methylpropanoic Acid*; *rac*-**1i**). From **3i** (6.91 g, 29.5 mmol) according to *Method C*. Recrystallization from H_2O gave 5.62 g (91%) of *rac*-**1i**. IR (KBr): 3150*m*, 2970*s*, 1600*s*, 1520*s*, 1400*s*, 1375*m*, 1330*m*, 1310*m*, 1260*s*, 1185*m*, 1130*m*, 1030*m*, 830*m*, 800*w*, 760*m*. ^{1}H-NMR (CD_3OD, 200 MHz): 7.2–6.85 (*m*, *AA'BB'*, J_{AB} = 9.0, 4 arom. H); 3.77 (*s*, MeO); 3.21, 2.86 (2*d*, *AB*, J_{AB} = 14.0, 2 H–C(3)); 1.43 (*s*, Me–C(2)). MS: 209 (1, $M^{+\cdot}$), 164 (8), 121 (100), 91 (15), 88 (40), 77 (20), 42 (54).

rac-*2,3-Dimethylvaline* [26] (= rac-*2-Amino-2,3,3-trimethylbutanoic Acid*; *rac*-**1k**). From **3k** (9.8 g, 57.6 mmol) according to *Method C*. Recrystallization from MeOH gave 6.98 g (83%) of *rac*-**1k**. IR (KBr): 3070*s*, 2950*s*, 1590*s*, 1520*s*, 1400*s*, 1385*s*, 1360*s*, 1250*w*, 1180*m*, 1130*m*, 880*w*, 825*m*, 790*w*. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 1.23 (*s*, Me–C(2)); 0.97 (*s*, *t*-Bu). MS: 145 (< 1, $M^{+\cdot}$), 100 (40), 91 (57), 89 (100), 71 (46), 57 (24), 43 (71), 42 (60).

rac-*2-Cyclopropylalanine* [26] (= rac-*2-Amino-2-cyclopropylpropanoic Acid*; *rac*-**1l**). From **3l** (10.0 g, 64.9 mmol) according to *Method C*. Recrystallization from MeOH/acetone gave 8.13 g (97%) of *rac*-**1l**. IR (KBr): 3450*m*, 3100*m*, 3020*s*, 1645*s*, 1600*s*, 1410*s*, 1400*s*, 1370*m*, 1305*m*, 1235*m*, 1155*m*, 1030*m*, 940*w*, 880*m*, 825*m*. ^{1}H-NMR (CD_3OD, 90 MHz): 1.60 (*s*, Me–C(2)); 1.45–1.15 ('*q*', $(CH_2)_2CH$); 0.95–0.65 (*m*, $(CH_2)_2CH$).

rac-N^2-*Acetyl-2-methylvaline Dimethylamide* (= rac-*2-Acetamido-*N^1,N^1*,2,3-tetramethylbutanamide*; **5**). To a stirred soln. of *rac*-3-(dimethylamino)-2-isopropyl-2-methyl-2*H*-azirine (550 mg, 3.92 mmol; **4**) [30] in MeCN (10 ml) was added under Ar at 0° AcOH (0.25 ml, 1.1 equiv.). The mixture was stirred for 18 h at r.t., the solvent evaporated, and the residue crystallized from Et_2O/hexane 1:2 and dried under reduced pressure: 680 mg (86.6%) of **5**. White solid. M.p. 180.5–181.5°. IR (KBr): 3333*m*, 2970*w*, 2933*w*, 1671*s*, 1618*s*, 1530*s*, 1443*w*, 1393*m*, 1288*w*,

1117*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 6.02 (br. *s*, 1 NH); 3.05 (*s*, $CONMe_2$); 2.17 (*sept.*, *J* = 6.8, Me_2CH); 2.01 (*s*, *Me*CONH); 1.51 (*s*, Me–C(2)); 0.96 (*t*, *J* = 6.8, Me_2CH). MS: 200 (< 1, $M^{+\cdot}$), 157 (7), 128 (32), 115 (32), 86 (100), 72 (16), 42 (35). Anal. calc. for $C_{10}H_{20}N_2O_2$ (200.28): C 59.97, H 10.07, N 13.99; found: C 59.73, H 10.31, N 14.08.

rac-*4-Methyl-2,4-diphenyl-1,3-oxazol-5(4*H*)-one* [31] (*rac*-**10n**). From **6** [31] (1.5 g, 5.88 mmol) and MeI according to *Method F*: 1.25 g (85%) of *rac*-**10n**. Colorless oil. A sample was crystallized from Et_2O/hexane at –20°. M.p. 50.3–53.5°. IR (KBr): 3060*w*, 2980*w*, 2930*w*, 1820*s*, 1655*s*, 1605*w*, 1580*w*, 1495*m*, 1450*m*, 1325*m*, 1295*m*, 1190*m*, 1180*m*, 1150*m*, 1090*m*, 1070*w*, 1030*m*, 1010*s*, 890*s*, 775*m*, 730*m*, 695*s*. ^{1}H-NMR ($CDCl_3$, 60 MHz): 8.2–7.15 (*m*, 10 arom. H); 1.87 (*s*, Me–C(4)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 179.2 (*s*, C(5)); 160.3 (*s*, C(2)); 139.0, 132.9, 128.9, 128.4, 128.2, 126.1, 125.6 (12 arom. C); 70.8 (*s*, C(4)); 21.1 (*q*, *Me*–C(4)). Anal. calc. for $C_{16}H_{13}NO_2$ (251.29): C 76.48, H 5.21, N 5.57; found: C 76.36, H 5.32, N 5.70.

rac-*4-Allyl-2,4-diphenyl-1,3-oxazol-5(4*H*)-one* (*rac*-**10o**) [30]. From **6** [31] (3.0 g, 11.8 mmol) and allyl bromide according to *Method F*: 2.61 g (80%) of *rac*-**10o**. Colorless oil which solidified. IR ($CHCl_3$): 3060*w*, 3020*w*, 2980*w*, 1818*s*, 1655*s*, 1570*w*, 1493*w*, 1450*w*, 1322*m*, 1298*m*, 1166*m*, 1050*m*, 970*m*, 930*m*, 892*w*, 698*w*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 8.2–7.95, 7.85–7.1 (2*m*, 10 arom. H); 5.95–5.4 (*m*, CH_2=C*H*CH_2); 5.3–4.95 (*m*, CH_2=$CHCH_2$); 3.05–2.8 (*m*, CH_2=$CHCH_2$). MS: 277 (< 1, $M^{+\cdot}$), 236 (23), 129 (5), 106 (8), 105 (100), 103 (5), 77 (35), 51 (12). Anal. calc. for $C_{18}H_{15}NO_2$ (277.33): C 77.96, H 5.45, N 5.05; found: C 78.24, H 5.63, N 5.05.

*Enantiomer (*R*)-***10o***.* From **21o** (6.17 g) according to *Method K*: 2.61 g (94%) of (*R*)-**10o**. $[\alpha]_D$ = –87.3 ($CHCl_3$, *c* = 1.0). IR, ^{1}H-NMR, and MS: in agreement with those of *rac*-**10o**.

*Enantiomer (*S*)-***10o***.* From **22o** (6.17 g) according to *Method K*: 2.55 g (92%) of (*S*)-**10o**. $[\alpha]_D$ = +83.7 ($CHCl_3$, *c* = 1.0). IR, ^{1}H-NMR, and MS: in agreement with those of *rac*-**10o**.

rac-*4-Benzyl-4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-one* (*rac*-**10p**) was synthesized from *N*-Benzoyl-DL-alanine (**7**; *Sigma*) according to [9].

*Enantiomer (*R*)-***10p***.* From **19p** (4.84 g) according to *Method K*: 2.36 g (89%) of (*R*)-**10p**. $[\alpha]_D$ = +86.1 ($CHCl_3$, *c* = 1.0). IR, ^{1}H-NMR, and MS: in agreement with those of *rac*-**10p**.

*Enantiomer (*S*)-***10p***.* From **20p** (4.84 g) according to *Method K*: 2.26 g (85%) of (*S*)-**10p**. $[\alpha]_D$ = –71.2 ($CHCl_3$, *c* = 1.0). IR, ^{1}H-NMR, and MS: in agreement with those of *rac*-**10p**.

rac-*2-Benzamido-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid* (*rac*-**11a**). From *rac*-**1a** (9.0 g, 47.1 mmol) according to *Method D*: 12.09 g (87%) of *rac*-**11a**. M.p. 209.8°. IR (KBr): 3300*w* (br.), 3063*w*, 3021*w*, 2921*w*, 2662*w* (br.), 1702*s*, 1637*s*, 1536*m*, 1491*w*, 1452*w*, 743*w*, 719*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.40 (br. *s*, 1 OH); 8.46 (br. *s*, 1 NH); 7.8–7.7 (*m*, 2 arom. H); 7.6–7.35 (*m*, 3 arom. H); 7.1 (*s*, 4 arom. H); 3.34, 3.20 (2*d*, *J* = 16.25, 2 aliph. H); 2.95–2.65 (*m*, 2 aliph. H); 2.55–2.4 (*m*, 1 aliph. H); 2.15–1.95 (*m*, 1 aliph. H). MS: 277 (< 1), 251 (2.2), 250 (1.5), 174 (42), 129 (78), 122 (100), 105 (82), 77 (58).

*Enantiomer (*R*)-***11a***.* To a stirred mixture of (*R*)-**12a** (see below; 1.3 g, 4.20 mmol) in THF/MeOH/H_2O 3:1:1 (34 ml) was added $LiOH \cdot H_2O$ (*Fluka*; 0.44 g, 10.5 mmol). The mixture was stirred at r.t. overnight, the pH adjusted to 7 with 2N aq. HCl, the solvent evaporated, and the residue extracted with 2N aq. HCl (50 ml) and AcOEt (100 ml). The org. phase was dried ($MgSO_4$) and evaporated, and the white solid dried overnight in a desiccator (P_2O_5) under high vacuum: 1.20 g (96.7%) of (*R*)-**12a**. M.p. 195–196°. $[\alpha]_D$ = –26.18 (MeOH, *c* = 0.5). IR (KBr): 3425*m*, 3326*m*, 2933*m*, 2588*w* (br.), 1715*s*, 1637*s*, 1577*m*, 1535*s*, 1490*m*, 1453*m*, 1298*m*, 742*m*, 717*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.40 (*s*, 1 COOH); 8.46 (*s*, 1 NH); 7.76 (*d*, *J* = 7.5, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.09 (*s*, 4 arom. H); 3.33, 3.19 (2*d*, *J* = 17.5, 2 aliph. H); 2.95–2.65 (*m*, 2 aliph. H); 2.55–2.4 (*m*, 1 aliph. H); 2.1–1.95 (*m*, 1 aliph. H). MS: 277 (< 1), 251 (4), 174 (44), 129 (85), 122 (100), 105 (99), 77 (77).

rac-*2-Benzamido-1,2,3,4-tetrahydro-5-methoxynaphthalene-2-carboxylic Acid* (*rac*-**11b**). From *rac*-**1b** (10.0 g, 45.2 mmol) according to *Method D*: 13.38 g (91%) of *rac*-**11b**. M.p. 227–228°. IR (KBr): 3350*w* (br.), 3005*w*, 2942*w* (br.), 2588*w* (br.), 1716*s*, 1623*m*, 1588*m*, 1538*s*, 1469*s*, 1282*m*, 1257*s*, 1220*m*, 1096*m*, 765*m*, 719*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.42 (br. *s*, COOH); 8.43 (br. *s*, NH); 7.8–7.7 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.15–7.0 (*m*, 1 arom. H); 6.8–6.65 (*m*, 2 arom. H); 3.75 (*s*, MeO); 3.30, 3.19 (2*d*, *J* = 17.7, 2 aliph. H); 2.75–2.55 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.1–1.9 (*m*, 1 aliph. H). MS: 325 (< 1, $M^{+\cdot}$), 204 (95), 159 (100), 144 (19), 122 (79) 105 (85), 77 (80), 51 (17).

rac-*2-Benzamido-1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylic Acid* (*rac*-**11c**). From *rac*-**1c** (5.0 g, 22.6 mmol) according to *Method D*: 6.25 g (85%) of *rac*-**11c**. M.p. 204–206°. IR (KBr): 3381*m*, 3055*w*, 3000*w*, 2999*w*, 1698*s*, 1662*s*, 1608*m*, 1578*w*, 1504*s*, 1434*w*, 1294*m*, 1266*m*, 1240*s*, 1157*w*, 1036*w*, 806*w*, 726*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.30 (br. *s*, COOH); 8.40 (br. *s*, NH); 7.8–7.7 (*m*, 2 arom. H); 7.6–7.35 (*m*, 3 arom. H); 7.05–6.95 (*m*, 1 arom. H); 6.75–6.6 (*m*, 2 arom. H); 3.70 (*s*, MeO); 3.22, 3.14 (2*d*, *J* = 16.5, 2 aliph. H); 2.95–2.6 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.1–1.95 (*m*, 1 aliph. H). MS: 325 (< 1, $M^{+\cdot}$), 204 (100), 159 (50), 105 (31), 77 (30), 57 (19), 49 (19).

rac-*2-Benzamido-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-carboxylic Acid* (*rac*-**11d**). From *rac*-**1d** (15.0 g, 67.8 mmol) according to *Method D*: 20.29 g (92%) of *rac*-**11d**. M.p. 247–248°. IR (KBr): 3306*m*, 3063*w*, 2994*w*, 2917*w*, 2836*w*, 1718*m*, 1698*s*, 1638*s*, 1611*m*, 1577*m*, 1540*s*, 1505*s*, 1449*m*, 1319*m*, 1254*s*, 1042*w*, 693*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.40 (br. *s*, COOH); 8.46 (br. *s*, NH); 7.8–7.7 (*m*, 2 arom. H); 7.6–7.35 (*m*, 3 arom. H); 7.05–6.95 (*m*, 1 arom. H); 6.75–6.6 (*m*, 2 arom. H); 3.70 (*s*, MeO); 3.30, 3.15 (2*d*, *J* = 17.2, 2 aliph. H); 2.85–2.55 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.1–1.9 (*m*, 1 aliph. H). MS: 325 (< 1, $M^{+\cdot}$), 204 (100), 159 (49), 105 (34), 77 (30). Anal. calc. for $C_{19}H_{19}NO_4$ (325.36): C 70.14, H 5.89, N 4.31; found: C 69.88, H 5.59, N 4.14.

rac-*2-Benzamido-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-carboxylic Acid* (*rac*-**11e**). From *rac*-**1e** (10.0 g, 45.2 mmol) according to *Method D*: 12.94 g (88%) of *rac*-**11e**. M.p. 237–238°. IR (KBr): 3290*m* (br.), 3063*w*, 2929*m*, 2835*w*, 1728*s*, 1704*s*, 1638*s*, 1586*m*, 1541*s*, 1469*s*, 1438*m*, 1257*s*, 1103*s*, 717*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.38 (br. *s*, COOH); 8.50 (br. *s*, NH); 7.85–7.75 (*m*, 2 arom. H); 7.6–7.35 (*m*, 3 arom. H); 7.15–7.0 (*m*, 1 arom. H); 6.8–6.65 (*m*, 2 arom. H); 3.76 (*s*, MeO); 3.13, 3.04 (2*d*, *J* = 17.3, 2 aliph. H); 2.95–2.6 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.05–1.9 (*m*, 1 aliph. H). MS: 325 (< 1, $M^{+\cdot}$), 204 (100), 159 (51), 105 (46), 77 (36).

rac-*2-Benzamido-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carboxylic Acid* (*rac*-**11f**). From *rac*-**1f** (10.0 g, 39.8 mmol) according to *Method D*: 12.02 g (85%) of *rac*-**11f**. M.p. 246–249°. IR (KBr): 3427*m* (br.), 3364*m*, 3084*w*, 3003*w*, 2955*w*, 2834*w*, 1711*s*, 1645*s*, 1577*w*, 1516*s*, 1486*m*, 1464*m*, 1256*s*, 1226*s*, 1115*m*, 718*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.38 (br. *s*, COOH); 8.40 (br. *s*, NH); 7.8–7.7 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 6.65 (*s*, 2 arom. H); 3.70 (*s*, MeO); 3.23, 3.09 (2*d*, *J* = 16.0, 2 aliph. H); 2.85–2.55 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.1–1.9 (*m*, 1 aliph. H). MS: 355 (< 1, $M^{+\cdot}$), 234 (100), 189 (25), 105 (28), 77 (34).

rac-*1-Benzamido-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid* (*rac*-**11g**). From *rac*-**1g** (13.0 g, 42.0 mmol) according to *Method D*: 10.54 g (85%) of *rac*-**11g**. A small sample was crystallized from AcOEt/hexane. M.p. 182–184°. IR (KBr): 3374*s*, 2932*w*, 2534*w* (br.), 1712*s*, 1615*s*, 1573*s*, 1517*s*, 1485*s*, 1446*w*, 1239*m*, 1214*m*, 735*s*, 624*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.65 (*s*, COOH); 8.61 (*s*, NH); 7.9–7.8 (*m*, 2 arom. H); 7.7–7.6 (*m*, 1 arom. H); 7.6–7.35 (*m*, 3 arom. H); 7.3–7.05 (*m*, 3 arom. H); 2.9–2.65 (*m*, 2 aliph. H); 2.5–2.35 (*m*, 2 aliph. H); 2.05–1.65 (*m*, 2 aliph. H). MS: 295 (< 1, $M^{+\cdot}$), 250 (11), 174 (27), 122 (32), 105 (100), 77 (44). Anal. calc. for $C_{18}H_{17}NO_3$ (295.32): C 73.20, H 5.80, N 4.74; found: C 73.08, H 5.79, N 4.70.

rac-*1-(4-Bromobenzamido)-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid* (*rac*-**11g′**). From *rac*-**1g** (0.4 g, 2.09 mmol) according to *Method D* (with 4-bromobenzoyl chloride): 0.62 g (79.3%) of *rac*-**11g′**. A small sample was crystallized from AcOEt/hexane. M.p. 194–196°. IR (KBr): 3420*w*, 3352*w*, 2941*w* (br.), 2551*w* (br.), 1729*s*, 1624*s*, 1589*m*, 1530*s*, 1481*s*, 1372*w*, 1252*s*, 1173*m*, 1010*w*, 757*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.66 (*s*, COOH); 8.73 (*s*, NH); 7.85–7.75 (*m*, 2 arom. H); 7.7–7.6 (*m*, 3 arom. H); 7.30–7.1 (*m*, 3 arom. H); 2.85–2.75 (*m*, 2 aliph. H); 2.5–2.4 (*m*, 2 aliph. H); 2.0–1.7 (*m*, 2 aliph. H). MS: 373 (< 1, $M^{+\cdot}$), 328 (15), 200 (14), 183 (81), 174 (100), 155 (24), 129 (63).

rac-*1-Benzamido-2,3-dihydro-6-methoxy-1*H*-indene-1-carboxylic Acid* (*rac*-**11h**). From *rac*-**1h** (5.0 g, 24.1 mmol) according to *Method D*: 6.52 g (87%) of *rac*-**11h**. M.p. 197–198°. IR (KBr): 3298*w* (br.), 3063*w*, 3001*m*, 2935*m*, 2631*w* (br.), 1719*s*, 1695*s*, 1637*s*, 1578*m*, 1518*s*, 1490*s*, 1288*s*, 1182*m*, 1031*w*, 715*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.5 (br. *s*, COOH); 7.85–7.75 (*m*, 2 arom. H); 7.55–7.4 (*m*, 3 arom. H); 7.22 (*d*, *J* = 8.3, 1 arom. H); 7.05–6.85 (*m*, 2 arom. H); 6.93 (br. *s*, 1 NH); 3.80 (*s*, MeO); 3.3–2.95 (*m*, 3 aliph. H); 2.6–2.45 (*m*, 1 arom. H). MS: 311 (< 1, $M^{+\cdot}$), 190 (71), 146 (57), 122 (27), 105 (100), 77 (79), 51 (18).

rac-N^2-*Acetyl-2,*O^4*-dimethyltyrosine* [26] (= rac-*2-Acetamido-3-(methoxyphenyl)-2-methylpropanoic Acid;* **11i**). From *rac*-**1i** (2.0 g, 9.6 mmol) according to *Method E*: 1.76 g (73%) of *rac*-**11i**. M.p. 177–178°. IR (KBr): 3360*s*, 2990*m*, 2960*m*, 2940*m*, 1712*m*, 1612*s*, 1552*s*, 1510*s*, 1460*m*, 1445*m*, 1390*m*, 1320*m*, 1300*m*, 1250*s*, 1180*m*, 1130*m*, 1032*m*, 840*m*, 822*w*, 790*w*, 765*w*, 660*m*. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 12.30 (br. *s*, COOH); 7.67 (br. *s*, NH); 7.15–6.75 (*m*, *AA′BB′*, 4 arom. H); 3.73 (*s*, MeO); 3.3–2.8 ('*q*', 2 H–C(3)); 1.80 (*s*, Ac); 1.18 (*s*, Me–C(2)). MS: 251 (2, $M^{+\cdot}$), 192 (26), 164 (3), 147 (5), 121 (100), 91 (8), 88 (10), 77 (12), 43 (20). Anal. calc. for $C_{13}H_{17}NO_4$ (251.27): C 62.14, H 6.82, N 5.57; found: C 62.40, H 6.70, N 5.60.

Enantiomer (R)-**11i** [26]. From **19i** (121 mg, 0.28 mmol) according to *Method L*. Crystallization from Et_2O gave 60 mg (85%) of (*R*)-**11i**. M.p. 185.8–186.8°. $[\alpha]_D = -60.4$ (MeOH, *c* = 0.95). Spectral data: in agreement with those of *rac*-**11i**.

Enantiomer (S)-**11i** [26]. From **20i** (280 mg, 0.65 mmol) according to *Method L*. Crystallization from Et_2O gave 148 mg (90%) of (*S*)-**11i**. M.p. 185.0–185.6°. $[\alpha]_D = +58.4$ (MeOH, *c* = 1.0). Spectral data: in agreement with those of *rac*-**11i**.

rac-N^2-*Acetyl-2,3-dimethylvaline* [26] (= rac-*2-Acetamido-2,3,3-trimethylbutanoic Acid*; *rac*-**11k**). From *rac*-**1k** (2.0 g, 13.8 mmol) according to *Method E*: 176 g (63%) of *rac*-**11k**. M.p. 195.3–195.7°. IR (KBr): 3380*s*, 2980*m*, 1710*s*, 1630*s*, 1530*s*, 1460*m*, 1440*m*, 1410*s*, 1370*s*, 1300*m*, 1250*s*, 1205*s*, 1160*m*, 1120*m*, 1010*w*, 980*w*, 840*m*, 780*m*, 660*m*. ^{1}H-NMR ((D$_6$)DMSO, 90 MHz): 11.90 (br. *s*, COOH); 7.33 (br. *s*, NH); 1.83 (*s*, Ac); 1.33 (*s*, Me–C(2));

0.97 (*s*, *t*-Bu). MS: 187 (< 1, M^+), 131 (24), 113 (61), 100 (49), 88 (57), 71 (31), 57 (100), 43 (95), 42 (91), 41 (84). Anal. calc. for $C_9H_{17}NO_3$ (187.24): C 57.73, H 9.15, N 7.48; found: C 57.64, H 8.87, N 7.50.

rac-N^2-*Acetyl-2-cyclopropylalanine* (= rac-*2-Acetamido-2-cyclopropylpropanoic Acid*; *rac*-**11l**). From *rac*-**11** (2.0 g, 15.5 mmol) according to *Method E*: 2.04 g (77%) of *rac*-**11l**. M.p. 185–186°. IR (KBr): 3570*s*, 3500*s*, 3360*s*, 3100*m*, 2990*m*, 1720*s*, 1650*s*, 1575*s*, 1465*m*, 1450*m*, 1390*m*, 1380*m*, 1330*m*, 1290*s*, 1240*s*, 1200*m*, 1160*m*, 1140*m*, 1040*m*, 990*m*, 935*m*. ^{1}H-NMR ((D$_6$)DMSO, 400 MHz): 12.00 (br. *s*, COOH); 7.98 (br. *s*, NH); 1.81 (*s*, Ac); 1.25–1.15 (*m*, $(CH_2)_2CH$); 1.14 (*s*, Me–C(2)); 0.4–0.3 (*m*, $(CH_2)_2CH$). MS: 171 (< 1, M^+), 126 (39), 98 (31), 88 (22), 70 (26), 68 (15), 57 (12), 43 (84), 42 (64). Anal. calc. for $C_8H_{13}NO_3$ (171.19): C 56.12, H 7.65, N 8.18; found: C 56.33, H 7.70, N 7.93.

rac-N^2-*Acetyl-2-methylvaline* (= rac-*2-Acetamido-2,3-dimethylbutanoic Acid*; *rac*-**11m**). A mixture of **5** (500 mg, 2.5 mmol) in dioxane (4 ml) and 4N aq. HCl (4 ml) was heated in a sealed tube at 70° for 1 h and then cooled to r.t. $CHCl_3$ (20 ml) and MeOH (4 ml) were added, the aq. phase was extracted with $CHCl_3$ (2 × 20 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue crystallized from AcOEt/hexane 1:2 and dried under reduced pressure: 295 mg (68.1%) of *rac*-**11m**. White solid. M.p. 192–194°. IR (KBr): 3347*s*, 2975*m*, 2634*w*, 1718*s*, 1623*s*, 1551*s*, 1443*m*, 1400*m*, 1374*w*, 1264*m*, 1159*m*, 862*w*, 657*w*, 621*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.08 (br. *s*, COOH); 7.71 (br. *s*, NH); 1.95 (*sept.*, *J* = 6.8, Me_2CH); 1.61 (*s*, Ac); 1.24 (*s*, Me–C(2)); 0.91, 0.84 (2*d*, *J* = 6.8, Me_2CH). MS: 174 (1, $[M + H]^+$), 130 (19), 128 (15), 88 (100), 86 (65), 72 (20), 60 (25), 43 (81), 42 (65).

Enantiomer (R)-**11m**. From **19m** (280 mg, 0.65 mmol) according to *Method L*. Crystallization from Et_2O gave 35 mg (91%) of (*R*)-**11m**. M.p. 196–197°. $[\alpha]_D = -1.3$ (MeOH, *c* = 1.0). Spectral data: in close agreement with those of *rac*-**11m**.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydronaphthalene-2-carboxylate* (*rac*-**12a**). From *rac*-**11a** (100 mg, 0.34 mmol) according to *Method P*: 92 mg (87.8%) of *rac*-**12a**. M.p. 139.5–140°. IR, ^{1}H-NMR, and MS: in close agreement with those of (*R*)- and (*S*)-**12a**. ^{1}H-NMR ($CDCl_3$, TAE): only partial signal separation; not used for double checking the optical purity.

Enantiomer (R)-**12a**. From 2.94 g (4.57 mmol) of **21a** according to *Method N*: 1.39 g (98%) of (*R*)-**12a**. Amorphous solid. M.p. 102.5–103°. $[\alpha]_D = -19.58$ (MeOH, *c* = 0.5). IR (KBr): 3354*w* (br.), 3061*w*, 2949*w*, 1843*s*, 1740*s*, 1529*s*, 1487*s*, 1300*m*, 1259*m*, 1220*m*, 1094*w*, 803*w*, 714*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.66 (*d*, *J* = 7, 2 arom. H); 7.48 (*t*, *J* = 7, 1 arom. H); 7.38 (*t*, *J* = 7, 2 arom. H); 7.2–7.1 (*m*, 4 arom. H); 6.26 (*s*, NH); 3.80 (*s*, MeO); 3.40, 3.14, (2*d*, *J* = 17, 2 aliph. H); 2.95–2.8 (*m*, 2 aliph. H); 2.75–2.7 (*m*, 1 aliph. H); 2.3–2.2 (*m*, 1 aliph. H). MS: 310 (< 1, M^+), 250 (5), 188 (61), 129 (76), 122 (100), 105 (90), 77 (52). Anal. calc. for $C_{19}H_{19}NO_3$ (309.35): C 73.77, H 6.19, N 4.53; found: C 73.80, H 6.29, N 4.52.

Enantiomer (S)-**12a**. From 1.27 g (1.98 mmol) of **22a** according to *Method N*: 0.58 g (94.6%) of (*S*)-**12a**. Amorphous solid. $[\alpha]_D = +19.82$ (MeOH, *c* = 0.5). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12a**.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydro-5-methoxynaphthalene-2-carboxylate* (*rac*-**12b**). From *rac*-**11b** (150 mg, 0.46 mmol) according to *Method P*: 140 mg (89.6%) of *rac*-**12b**. M.p. 135.5–136.5°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12b**. ^{1}H-NMR ($CDCl_3$, TAE): rather poor signal separation; not used for double checking the optical purity.

Enantiomer (R)-**12b**. From 5.0 g (7.43 mmol) of **21b** according to *Method N*: 2.42 g (96%) of (*R*)-**12b**. Amorphous solid. $[\alpha]_D = -28.5$ ($CHCl_3$, *c* = 0.2). IR (KBr): 3309*w*, 3258*w*, 3058*w*, 3005*w*, 2946*w*, 2890*w*, 2838*w*, 1745*s*, 1720*s*, 1642*s*, 1586*m*, 1543*s*, 1468*s*, 1437*w*, 1315*m*, 1289*m*, 1259*s*, 1216*m*, 1097*s*, 762*m*, 714*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.7–7.6 (*m*, 2 arom. H); 7.55–7.3 (*m*, 3 arom. H); 7.14 (*t*, *J* = 7.2, 1 arom. H); 6.8–6.7 (*m*, 2 arom. H); 6.27 (br. *s*, 1 NH): 3.82, 3.79 (2*s*, 2 MeO); 3.39, 3.16 (2*d*, *J* = 16.4, 2 aliph. H); 2.25–2.1 (*m*, 1 aliph. H). MS: 339 (2, M^+), 280 (4), 218 (100), 159 (93), 122 (55), 105 (78), 77 (60).

Enantiomer (S)-**12b**. From 18.0 g (26.8 mmol) of **22b** according to *Method N*: 8.86 g (97.6%) of (*S*)-**12b**. Amorphous solid. $[\alpha]_D = +26.5$ ($CHCl_3$, *c* = 0.2). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12b**.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylate* (*rac*-**12c**). From *rac*-**11c** (135 mg, 0.42 mmol) according to *Method P*: 137 mg (96%) of *rac*-**12c**. M.p. 130–131°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12c**. ^{1}H-NMR ($CDCl_3$, TAE): base-line splitting of one of the MeO signals; used to double check the enantiomeric puritiy.

Enantiomer (R)-**12c**. From **21c** (5.0 g, 7.43 mmol) according to *Method M*: 2.32 g (92%) of (*R*)-**12c**. Amorphous solid. $[\alpha]_D = -68.0$ ($CHCl_3$, *c* = 0.4). IR (KBr): 3357*w* (br.), 3060*w*, 2997*w*, 2950*w*, 2836*w*, 1740*s*, 1645*m* (br.), 1611*w*, 1527*m*, 1503*s*, 1434*m*, 1295*m*, 1267*m*, 1234*s*, 1046*m*, 715*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.7–7.6 (*m*, 2 arom. H); 7.5–7.35 (*m*, 3 arom. H); 7.05 (*d*, *J* = 8.0, 1 arom. H); 6.8–6.7 (*m*, 1 arom. H); 6.7–6.65 (*m*, 1 arom. H); 6.25 (br. *s*, 1 NH); 3.80, 3.79 (2*s*, 2 MeO); 3.30 (*d*, *J* = 16.4, 1 aliph. H); 3.06 (br. *d*, *J* = 16.4, 1 aliph. H); 2.9–2.7 (*m*, 3 aliph. H); 2.3–2.15 (*m*, 1 aliph. H). MS: 339 (< 1, M^+), 280 (4), 218 (100), 159 (36), 105 (45), 77 (46).

Enantiomer (S)-**12c**. From **22c** (5.0 g, 7.43 mmol) according to *Method M*: 2.37 g (94%) of (*S*)-**12c**. Amorphous solid. $[\alpha]_D = +67.7$ ($CHCl_3$, $c = 0.3$). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12c**.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-carboxylate* (*rac*-**12d**). From *rac*-**11d** (500 mg, 1.54 mmol) according to *Method P*: 450 mg (86%) of *rac*-**12d**. M.p. 167–168°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12d**. ^{1}H-NMR ($CDCl_3$, TAE): partial signal separation; not used to double check the enantiomeric purity.

Enantiomer (R)-**12d**. From **19d** (6.0 g, 11.4 mmol) according to *Method M*: 3.73 g (96.4%) of (*R*)-**12d**. Amorphous solid. $[\alpha]_D = -118.3$ ($CHCl_3$, $c = 0.4$). IR (KBr): 3360*w*, 3059*w*, 2998*w*, 2949*w*, 2838*w*, 1739*s*, 1644*s*, 1579*m*, 1528*s*, 1504*s*, 1449*m*, 1298*m*, 1255*s*, 1035*m*, 717*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.7–7.6 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.06 (*d*, $J = 7.9$, 1 arom. H); 6.8–6.75 (*m*, 1 arom. H); 6.7–6.65 (*m*, 1 arom. H); 6.29 (br. *s*, 1 NH); 3.79, 3.78 (2*s*, 2 MeO); 3.40 (*d*, $J = 17.9$, 1 aliph. H); 3.10 (br. *d*, $J = 17.9$, 1 aliph. H); 2.85–2.65 (*m*, 3 aliph. H); 2.3–2.15 (*m*, 1 aliph. H). MS: 339 (< 1, M^+), 280 (4), 218 (100), 159 (58), 105 (76), 77 (86), 51 (20).

Enantiomer (S)-**12d**. From **20d** (10.0 g, 19.0 mmol) according to *Method M*: 5.93 (92%) of (*S*)-**12d**. Amorphous solid. $[\alpha]_D = +116.5$ ($CHCl_3$, $c = 0.2$). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12d**. (*S*)-**12d** was also obtained by treatment of **22d** according to *Method N*.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-carboxylate* (*rac*-**12e**). From *rac*-**11e** (150 mg, 0.46 mmol) according to *Method P*: 133 mg (85%) of *rac*-**12e**. M.p. 159–160°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12e**. ^{1}H-NMR ($CDCl_3$, TAE): base-line splitting of one of the MeO signals; used to double check the enantiomeric purity.

Enantiomer (R)-**12e**. From **21e** (10.0 g, 14.86 mmol) in MeOH according to *Method N*: 4.68 (92.7%) of (*R*)-**12e**. Amorphous solid. $[\alpha]_D = -142.5$ ($CHCl_3$, $c = 0.2$). IR (KBr): 3366*w* (br.), 3062*w*, 2998*w*, 2948*w*, 1739*s*, 1647*s*, 1586*m*, 1527*s*, 1468*s*, 1437*m*, 1292*m*, 1259*s*, 1099*m*, 1047*m*, 774*w*, 713*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.75–7.65 (*m*, 2 arom. H); 7.55–7.3 (*m*, 3 arom. H); 7.16 (*t*, $J = 7.9$, 1 arom. H); 6.8–6.65 (*m*, arom. H); 6.20 (br. *s*, 1 NH); 3.83, 3.80 (2*s*, MeO); 3.20, 3.02 (2 br. *d*, $J = 17.8$, 2 aliph. H); 2.95–2.75 (*m*, 3 aliph. H); 2.8–2.6 (*m*; 1 aliph. H). MS: 339 (< 1, M^+), 280 (4), 218 (100), 159 (48), 105 (42), 77 (32).

Enantiomer (S)-**12e**. From **22e** (10.0 g, 14.86 mmol) according to *Method N*: 4.73 g (93.7%) of (*S*)-**12e**. Amorphous solid. $[\alpha]_D = +138.5$ ($CHCl_3$, $c = 0.2$). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12e**.

rac-*Methyl 2-Benzamido-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carboxylate* (*rac*-**12f**). From *rac*-**11f** (150 mg, 0.42 mmol) according to *Method P*: 137 mg (88%) of *rac*-**12f**. M.p. 195.5–201.5°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12f**. ^{1}H-NMR ($CDCl_3$, TAE): base-line splitting of one of the MeO signals; used to double check the enantiomeric purity.

Enantiomer (R)-**12f**. From **21f** (5.0 g, 7.11 mmol) according to *Method N*: 2.45 g (93.4%) of (*R*)-**12f**. Amorphous solid. $[\alpha]_D = -90.0$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3358*w* (br.), 3060*w*, 2947*w*, 2836*w*, 1740*s*, 1658*m* (br.), 1580*w*, 1516*s*, 1487*m*, 1449*m*, 1356*w*, 1244*s*, 1115*m*, 1049*m*, 715*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.7–7.65 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 6.63, 6.59 (2*s*, 2 arom. H); 6.27 (br. *s*, 1 NH); 3.86, 3.80 (2*s*, MeO); 3.33, 3.04 (2 br. *d*, $J = 16.1$, 2 aliph. H); 2.85–2.65 (*m*, 3 aliph. H); 2.3–2.15 (*m*, 1 aliph. H). MS: 369 (< 1, M^+), 248 (100), 189 (23), 105 (31), 77 (31).

Enantiomer (S)-**12f**. From **22f** (5.0 g, 7.11 mmol) according to *Method N*: 2.42 g (92%) of (*S*)-**12f**. Amorphous solid. $[\alpha]_D = +92.0$ ($CHCl_3$, $c = 0.1$). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12f**.

rac-*Methyl 1-Benzamido-1,2,3,4-tetrahydronaphthalene-1-carboxylate* (*rac*-**12g**). From *rac*-**11g** (200 mg, 0.68 mmol) according to *Method P*: 191 mg (91.0%) of *rac*-**12g**. M.p. 125.5°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12g**. ^{1}H-NMR ($CDCl_3$, TAE): MeO signal splitted; used to double check the enantiomeric purity.

Enantiomer (R)-**12g**. From **21g** (1.85 g, 2.88 mmol) according to *Method M*: 0.78 g (91.8%) of (*R*)-**12g**. Amorphous solid. $[\alpha]_D = -71.0$ (MeOH, $c = 1.0$). IR (KBr): 3405*m*, 3346*m*, 2946*w*, 1724*s*, 1646*s*, 1578*m*, 1517*s*, 1483*s*, 1314*m*, 1228*m*, 1023*w*, 714*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.78 (*d*, $J = 8$, 2 arom. H); 7.55–7.35 (*m*, 4 arom. H); 7.3–7.15 (*m*, 3 arom. H); 7.06 (*s*, NH); 3.77 (*s*, MeO); 3.05–2.7 (*m*, 3 aliph. H); 2.6–2.4 (*m*, 1 aliph. H); 2.2–1.8 (2*m*, 2 aliph. H). MS: 309 (< 1, M^+), 250 (24), 188 (23), 105 (100), 77 (37). Anal. calc. for $C_{19}H_{19}NO_3$ (309.35): C 73.77, H 6.19, N 4.53; found: C 73.9, H 6.36, N 4.55.

Enantiomer (S)-**12g**. From **22g** (1.96 g, 3.05 mmol) according to *Method M*: 0.76 g (84.1%) of (*S*)-**12g**. Amorphous solid. $[\alpha]_D = +69.3$ (MeOH, $c = 1.0$). IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)-**12g**.

rac-*Methyl 1-Benzamido-2,3-dihydro-1*H*-indene-1-carboxylate* (*rac*-**12h**). From *rac*-**11h** (200 mg, 0.64 mmol) according to *Method P*: 195 mg (93.6%) of *rac*-**12h**. M.p. 163–164°. IR, ^{1}H-NMR, and MS: in agreement with those of (*R*)- and (*S*)-**12h**. ^{1}H-NMR ($CDCl_3$, TAE): base-line splitting of one of the MeO signals; used to double check the enantiomeric purity.

Enantiomer (R)-**12h**. From **21h** (10.0 g, 15.18 mmol) according to *Method N*: 4.64 (94%) of (*R*)-**12h**. Amorphous solid. $[\alpha]_D = -156.3$ ($CHCl_3$, $c = 0.3$). IR (KBr): 3327*w* (br.), 3061*w*, 3000*w*, 2950*w*, 2838*w*, 1735*s*, 1631*s*, 1577*w*, 1519*s*, 1486*s*, 1288*m*, 1242*m*, 1167*w*, 1067*w*, 1031*w*, 717*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.85–7.75 (*m*, 2 arom. H); 7.6–7.4 (*m*, 3 arom. H); 7.22 (*d*, $J = 7.9$, 1 arom. H); 6.96 (br. *s*, NH); 6.95–6.85 (*m*, 2 arom. H); 3.80, 3.75 (2*s*, 2 MeO); 3.3–3.05 (*m*, 3 aliph. H); 2.65–2.5 (*m*, 1 aliph. H). MS: 325 (1, $M^{+\cdot}$), 204 (100), 145 (23), 105 (98), 77 (43).

Enantiomer (S)-**12h**. From **22h** (10.0 g, 15.18 mmol) according to *Method N*: 4.67 g (94.5%) of (*S*)-**12h**. Amorphous solid. A sample was crystallized from hexane. M.p. 107–108°. $[\alpha]_D = +156.7$ ($CHCl_3$, $c = 0.3$). IR, ^{1}H-NMR, MS: in agreement with those of (*R*)-**12h**.

(R)-N^2-Acetyl-2,3-dimethylvaline Methyl Ester (= (R)-Methyl 2-Acetamido-2,3,3-trimethylbutanoate; (*R*)-**12k**). From **19k** (102 mg, 0.28 mmol) according to *Method M*. Crystallization from Et_2O gave 52 mg (92%) of (*R*)-**12k**. M.p. 106.4–107.2°. $[\alpha]_D = -11.3$ ($CHCl_3$, $c = 0.45$). IR (KBr): 3470*m*, 2990*m*, 1735*s*, 1670*s*, 1500*s*, 1445*m*, 1410*m*, 1380*m*, 1290*m*, 1270*m*, 1160*m*, 1120*s*, 980*w*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 6.0 (br. *s*, NH); 3.70 (*s*, MeO); 2.00 (*s*, Ac); 1.63 (*s*, Me–C(2)); 1.03 (*s*, *t*-Bu). MS: 201 (< 1, $M^{+\cdot}$), 145 (21), 113 (32), 102 (96), 100 (99), 85 (13), 70 (11), 57 (25), 41 (100). Anal. calc. for $C_{10}H_{19}NO_3$ (201.26): C 59.67, H 9.52, N 6.96; found: C 59.51, H 9.77, N 6.78.

Enantiomer (S)-**12k**. From **20k** (115 mg, 0.32 mmol) according to *Method M*. Crystallization from Et_2O gave 59 mg (92%) of (*S*)-**12k**. M.p. 105.9–106.6°. $[\alpha]_D = +10.8$ ($CHCl_3$, $c = 1.0$). Spectral data: in agreement with those of (*R*)-**12k**.

(R)-N^2-Acetyl-2-cyclopropylalanine Methyl Ester (= (R)-Methyl 2-Acetamido-2-cyclopropylpropanoate; (*R*)-**12l**). From **19l** (133 mg, 0.39 mmol) according to *Method M*: 68 mg (95%) of (*R*)-**12l**. Colorless oil. $[\alpha]_D = -13.0$ ($CDCl_3$, $c = 0.92$). IR ($CHCl_3$): 3450*m*, 3000*m*, 2960*m*, 2880*m*, 1740*s*, 1680*s*, 1500*s*, 1450*m*, 1385*m*, 1295*m*, 1270*m*, 1155*m*, 1130*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 6.30 (br. *s*, NH); 3.73 (*s*, MeO); 2.0 (*s*, Ac); 1.40 (*s*, Me–C(2)); 1.35–1.2 (*m*, $(CH_2)_2CH$); 0.55–0.35 (*m*, $(CH_2)_2CH$). MS: 185 (< 1, $M^{+\cdot}$), 144 (3), 142 (8), 126 (52), 102 (20), 98 (23), 84 (100), 43 (60), 42 (33).

Enantiomer (S)-**12l**. From **20l** (164 mg, 0.48 mmol) according to *Method M*: 78 mg (88%) of (*S*)-**12l**. Colorless oil. $[\alpha]_D = +11.0$ ($CDCl_3$, $c = 0.69$). Spectral data: in agreement with those of (*R*)-**12l**.

(R)-N^2-Acetylvaline ((*R*)-**13** (= (*R*)-**11q**)). From **19q** (220 mg, 0.66 mmol) according to *Method O* (2 h). Crystallization from CH_2Cl_2 gave 99 mg (94%) of (*R*)-**13**. M.p. 167.9–168.3°. $[\alpha]_D = -20.4$ (H_2O, $c = 1.0$). Spectral data: in close agreement with those of *rac*-**13**.

Enantiomer (S)-**13** (= (*S*)-**11q**). From **20q** (200 mg, 0.60 mmol) according to *Method O* (2 h). Crystallization from CH_2Cl_2 gave 87 mg (91%) of (*S*)-**13**. M.p. 167.6–168.8°. $[\alpha]_D = +19.8$ (H_2O, $c = 1.0$). Spectral data: in close agreement with those of *rac*-**13**.

N^2-[(R)-2-Benzamido-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-carbonyl]-L-phenylalanine N^1,N^1-(Tetramethylene)amide (**19d**) *and (S,S)-Isomer* **20d**. From *rac*-**11d** (10.0 g, 30.73 mmol) and **16** in the presence of *N*-methyl morpholine (5.1 ml, 46.3 mmol) according to *Method H*. The residue was suspended in AcOEt/hexane 3:1 (100 ml), stirred for 1 h, filtered, and dried under reduced pressure: 6.78 g (42%) of **20d**. The filtrate was evaporated and the residue chromatographed (SiO_2 (900 g), Et_2O/i-PrOH 93:7): 7.10 g (44%) of **19d** as an amorphous solid. A sample of **19d** was recrystallized from AcOEt/hexane. M.p. 174.5–175.5°. R_f (Et_2O/i-PrOH 92:8) 0.49. $[\alpha]_D = -39.4$ (EtOH, $c = 0.5$). IR (KBr): 3424*w*, 3304*w* (br.), 3027*w*, 2943*w*, 2840*w*, 1676*s*, 1630*s*, 1505*s*, 1449*s*, 1342*w*, 1294*m*, 1255*m*, 1160*w*, 1031*w*, 811*w*, 699*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz); 8.13 (br. *s*, NH); 7.8–7.7 (*m*, 1 NH, 2 arom. H); 7.6–7.4 (*m*, 3 arom. H); 7.16 (*s*, 5 arom. H); 6.96 (*d*, $J = 8.8$, 1 arom. H); 6.7–6.6 (*m*, 1 arom. H); 6.6–6.55 (*m*, 1 arom. H); 4.75–4.6 (*m*, H–C(2.2)); 3.70 (*s*, MeO); 3.55–3.35 (*m*, 1 aliph. H); 3.3–3.0 (*m*, 5 aliph. H); 2.95–2.75 (*m*, 2 aliph. H); 2.7–2.55 (*m*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 2.05–1.85 (*m*, 1 aliph. H); 1.85–1.55 (*m*, 4 aliph. H); FAB-MS: 525 (< 1, $[M + H]^+$), 404 (14), 333 (14), 280 (16), 187 (72), 158 (20), 105 (100), 77 (26), 72 (54).

Further elution yielded 0.48 g (3%) of **20d** (total amount 7.26 g (45%)). M.p. 206–207°. R_f (Et_2O/i-PrOH 92:8) 0.45. $[\alpha]_D = +26.7$ (EtOH, $c = 0.6$). IR (KBr): 3372*m*, 3304*m*, 3029*w*, 2940*w*, 2839*w*, 1655*s*, 1638*s*, 1581*w*, 1534*s*, 1502*s*, 1447*s*, 1342*w*, 1294*w*, 1253*m*, 1160*w*, 1032*w*, 702*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.13 (br. *s*, NH); 7.85–7.7 (*m*, 1 NH, 2 arom. H); 7.6–7.4 (*m*, 3 arom. H); 7.17 (*s*, 5 arom. H); 6.93 (*d*, $J = 8.4$, 1 arom. H); 6.7–6.55 (*m*, 2 arom. H); 4.8–4.65 (*m*, H–C(2.2)); 3.68 (*s*, MeO); 3.6–3.4 (*m*, 1 aliph. H); 3.35–3.0 (*m*, 6 aliph. H); 2.95–2.75 (*m*, 2 aliph. H); 2.65–2.35 (*m*, 3 aliph. H); 2.0–1.55 (*m*, 5 aliph. H). FAB-MS: 525 (< 1, $[M + H]^+$), 404 (16), 333 (16), 280 (16), 187 (77), 158 (22), 105 (100), 77 (26), 72 (64).

*N^2-[(S)-2-Benzamido-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carbonyl-L-phenylalanine N^1,N^1-(Tetramethylene)amide (***20f**). From *rac*-**11f** (692 mg, 1.95 mmol) and **16** according to *Method H*. The residue was crystallized from AcOEt/hexane: 445 mg (41%) of **20f**. M.p. 179.1–181.4°. A sample was recrystallized from AcOEt/hexane to give suitable crystals for X-ray analysis. $[\alpha]_D = +72.5$ ($CHCl_3$, $c = 0.4$). IR (KBr): 3387*m*,

3289*w*, 2843*w*, 2881*w*, 1660*s*, 1642*s*, 1515*s*, 1446*s*, 1289*w*, 1222*m*, 1115*m*, 1029*w*, 858*w*, 687*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.65–7.55 (*m*, 2 arom. H); 7.5–7.15 (*m*, 8 arom. H, 1 NH); 6.60, 6.58 (2*s*, 2 arom. H); 6.24 (br. *s*, 1 NH); 4.95–4.85 (*m*, H–C(2.2)); 3.86, 3.85 (2*s*, 2 MeO); 3.45–3.2 (*m*, 4 aliph. H); 3.15–2.55 (*m*, 7 aliph. H); 2.25–2.05 (*m*, 1 aliph. H); 1.85–1.5 (*m*, 4 aliph. H). FAB-MS: 556 (12, $[M + H]^+$), 339 (10), 311 (10), 218 (30), 120 (30), 105 (100). Anal. calc. for $C_{33}H_{37}N_3O_5$ (555.68): C 71.33, H 6.71, N 7.56; found: C 71.07, H 6.59, N 7.55.

N^2-*[(*R*)-1-Benzamido-1,2,3,4-tetrahydronaphthalene-1-carbonyl]*-L-*phenylalanine* N^1,N^1-*(Tetramethylene)-amide* (**19g**) *and (*S,S*)-Isomer* **20g**. From *rac*-**11g** (500 mg, 1.69 mmol and **16** according to *Method H*. The residue was chromatographed (SiO_2 (100 g), Et_2O/i-PrOH 95:5): 400 mg (48%) of **19g** as an amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 81–82°. R_f (Et_2O/i-PrOH 92:8) 0.54. $[\alpha]_D = -11.0$ (MeOH, $c = 0.3$). IR (KBr): 3383*m*, 3060*w*, 3026*w*, 2930*w*, 2873*w*, 1641*s* (br.), 1502*s*, 1476*s*, 1448*s*, 1187*w*, 747*w*, 701*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.87 (*s*, 1 NH); 7.79 (*d*, $J = 8$, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.35–7.05 (*m*, 9 arom. H); 6.23 (*d*, $J = 7$, 1 NH); 4.8 (*m*, 1 aliph. H); 3.45–3.2 (*m*, 3 aliph. H); 3.15–2.6 (*m*, 6 aliph. H); 2.1–1.55 (*m*, 7 aliph. H). FAB-MS: 495 (< 1, $[M + H]^+$), 374 (< 1), 250 (62), 245 (12), 105 (100), 77 (19).

Further elution yielded 362 mg (43%) of **20g** as an amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 79.5–80°. R_f (Et_2O/i-PrOH 92:8) 0.49. $[\alpha]_D = +18.0$ (MeOH, $c = 0.3$). IR (KBr): 3389*w* (br.), 3060*w*, 3026*w*, 2950*w*, 2873*w*, 1642*s* (br.), 1503*s*, 1476*s*, 1448*s*, 1188*w*, 743*w*, 701*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.97 (*s*, 1 NH); 7.80 (*d*, $J = 6$, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.3–7.15 (*m*, 5 arom. H); 7.15–7.05 (*m*, 2 arom. H); 7.05–6.9 (*m*, 2 arom. H); 6.13 (*d*, $J = 8$, 1 NH); 4.88 (*m*, H–C(2.2)); 3.55–3.25 (*m*, 3 aliph. H); 3.15–2.95 (*m*, 1 aliph. H); 2.95–2.7 (*m*, 5 aliph. H); 2.15–1.5 (*m*, 7 aliph. H). FAB-MS: 495 (< 1, $[M + H]^+$), 374 (< 1), 178 (3), 250 (62), 245 (12), 105 (100), 77 (19).

N^2-*[(*R*)-N^2-Acetyl-2,O^4-dimethyltyrosyl]*-L-*phenylalanine Dimethylamide* (**19i**) *and* (S,S*)-Isomer* **20i**. From *rac*-**11i** (500 mg, 2.0 mmol) in THF (3 ml) and **15** according to *Method G* (24 h). The residue was chromatographed (Et_2O/i-PrOH 4:1): 319 mg (37%) of **19i**. M.p. 190.3–190.6°. R_f (Et_2O/i-prOH 4:1) 0.43. $[\alpha]_D = +12.0$ ($CHCl_3$, $c = 0.95$). IR (KBr): 3380*m*, 3310*m*, 3040*w*, 2940*m*, 1680*s*, 1660*s*, 1640*s*, 1540*s*, 1515*s*, 1460*s*, 1420*m*, 1370*m*, 1305*m*, 1255*s*, 1180*m*, 1140*m*, 1040*m*, 850*m*, 820*w*, 760*w*, 710*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.3–6.75 (*m*, 1 NH, 9 arom. H); 6.19 (br. *s*, 1 NH); 5.15–5.05 (*m*, *ABX*, H–C(2.2)); 3.76 (*s*, MeO); 3.35–3.15 (*m*, *AB*, $J_{AB} = 14.0$, 2 H–C(3.1)); 3.05–2.95 (*m*, *ABX*, 2 H–C(3.2)); 2.87, 2.65 (2*s*, Me_2N); 1.96 (*s*, Ac); 1.50 (*s*, Me–C(2.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.7, 170.6, 169.5 (3*s*, 3 amide CO); 158.1, 135.9, 130.8, 129.1, 128.1, 126.7, 113.2 (12 arom. C); 60.5 (*s*, C(2.1)); 54.9 (*q*, MeO); 50.3 (*d*, C(2.2)); 39.6, 39.2 (2*t*, C(3.2), C(3.1)); 36.6, 35.4 (2*q*, Me_2N); 23.8, 23.5 (2*q*, *Me*–C(2.1), *Me*CO). MS 427 (< 1, $M^{+\cdot}$), 366 (37), 321 (11), 294 (17), 286 (27), 262 (16), 206 (27), 189 (36), 175 (98), 164 (92), 121 (97), 91 (48), 77 (18), 72 (44), 46 (100), 43 (43). Anal. calc. for $C_{24}H_{33}N_3O_4$ (427.53): C 67.42, H 7.78, N 9.83; found: C 67.78, H 7.65, N 9.83.

Further elution yielded 303 mg (35%) of **20i**. M.p. 154.5–155.3°. R_f (Et_2O/i-PrOH 4:1) 0.32. $[\alpha]_D = +36.3$ ($CHCl_3$, $c = 1.18$). IR (KBr): 3390*s*, 3310*s*, 3040*m*, 2945*m*, 1680*s*, 1660*s*, 1635*s*, 1545*s*, 1515*s*, 1460*s*, 1420*m*, 1380*m*, 1300*m*, 1250*s*, 1180*m*, 1145*m*, 1035*m*, 850*m*, 720*m*, 700*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.3–6.75 (*m*, 1 NH, 9 arom. H); 6.02 (br. *s*, 1 NH); 5.15–5.05 (*m*, *ABX*, H–C(2.2)); 3.76 (*s*, MeO); 3.4–3.15 (*m*, *AB*, $J_{AB} = 14.0$, 2 H–C(3.1)); 3.05–2.95 (*m*, *ABX*, 2 H–C(3.2)); 2.85, 2.61 (2*s*, Me_2N); 1.94 (*s*, Ac); 1.52 (*s*, Me–C(2.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.8, 170.6, 169.4 (3*s*, 3 CO); 158.1, 136.1, 130.8, 129.1, 128.1, 126.7, 113.2 (12 arom. C); 60.4 (*s*, C(2.1)); 54.9 (*q*, MeO); 50.5 (*d*, C(2.2)); 40.0, 39.0 (2*t*, C(3.2), C(3.1)); 36.6, 35.4 (2*q*, Me_2N); 23.8, 23.3 (2*q*, *Me*–C(2.1), *Me*CO). MS 427 (< 1, $M^{+\cdot}$), 366 (34), 321 (11), 294 (18), 286 (20), 262 (14), 206 (29), 189 (31), 175 (100), 164 (99), 121 (98), 91 (46), 77 (17), 72 (42), 46 (99), 43 (44). Anal. calc. for $C_{24}H_{33}N_3O_4$ (427.53): C 67.42, H 7.78, N 9.83; found: C 67.58, H 7.76, N 9.89.

N^2-*[(*R*)-N^2-Acetyl-2,3-dimethylvalyl]*-L-*phenylalanine Dimethylamide* (**19k**) *and (*S,S*)-Isomer* **20k**. From *rac*-**11k** (900 mg, 4.8 mmol) in CH_2Cl_2 (10 ml) and **15** according to *Method G* (67 h at r.t.). The residue was suspended in Et_2O (15 ml), stirred for 1 h, and filtered. The filtrate was evaporated and dried: 776 mg (41%) of the imidazolidin-4-ones (which will be described later). The Et_2O-insoluble fraction was chromatographed (Et_2O/i-PrOH 4:1): 201 mg (12%) of **19k**. M.p. > 206° (dec.). R_f (Et_2O/i-PrOH 4:1) 0.43. $[\alpha]_D = +19.9$ ($CHCl_3$, $c = 0.93$). IR (KBr): 3410*m*, 3330*m*, 2980*m*, 2960*m*, 1670*s*, 1650*s*, 1635*s*, 1500*m* 1440*m*, 1400*s*, 1270*w*, 1145*w*, 1090*w*, 930*w*, 730*s*, 705*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.27 (*s*, 5 arom. H); 6.74 (br. *d*, $J = 7.0$, 1 NH); 6.0 (br. *s*, 1 NH); 5.25–5.0 (*m*, *ABX*, H–C(2.2)); 3.25–2.75 (*m*, *ABX*, 2 H–C(3.2)); 2.84, 2.52 (2*s*, Me_2N); 2.0 (*s*, Ac); 1.66 (*s*, 1 Me–C(2.1)); 1.01 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 100 MHz): 171.2, 171.1, 169.9 (3*s*, 3 CO); 136.1, 129.1, 128.1, 126.7 (6 arom. C); 65.3 (*s*, C(2.1)); 50.5 (*d*, C(2.2)); 39.5 (*t*, C(3.2)); 36.7, 35.4 (2*q*, Me_2N); 36.5 (*s*, Me_3C); 25.6 (*q*, Me_3C); 23.8 (*q*, *Me*CO); 17.0 (*q*, Me–C(2.1)). MS: 361 (1, $M^{+\cdot}$), 287 (65), 242 (49), 214 (90), 176 (81), 143 (63), 131 (38), 121 (36), 104 (91), 101 (84), 91 (42), 83 (38), 77 (23), 72 (100), 57 (51), 41 (87). Anal. calc. for $C_{20}H_{31}N_3O_3$ (361.48): C 66.45, H 8.64, N 11.63; found: C 66.37, H 8.40, N 11.84.

Further elution yielded 185 mg (11%) of **20k**. M.p. 219.5–219.8°. R_f (Et_2O/i-PrOH 4:1) 0.26. $[\alpha]_D = +22.6$

($CHCl_3$, $c = 0.6$). IR (KBr): 3390*m*, 3330*s*, 2980*m*, 2960*m*, 2935*m*, 1675*s*, 1660*s*, 1635*s*, 1500*s*, 1405*s*, 1365*m*, 1285*m*, 1135*m*, 1095*w*, 730*m*, 700*m*, 680*w*, 640*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.24 (*s*, 5 arom. H); 6.78 (br. *d*, $J = 7.0$, 1 NH); 6.11 (br. *s*, 1 NH); 5.25–5.0 (*m*, *ABX*, H–C(2.2)); 3.25–2.8 (*m*, *ABX*, 2 H–C(3.2)); 2.84, 2.60 (2*s*, Me_2N); 1.98 (*s*, Ac); 1.62 (*s*, *Me*–C(2.1)); 1.01 (*s*, *t*-Bu). MS 361 (6, M^+), 305 (5), 287 (73), 242 (39), 214 (81), 176 (61), 142 (88), 131 (20), 120 (64), 104 (48), 100 (100), 91 (26), 83 (24), 77 (11), 72 (78), 57 (35), 46 (38), 41 (47). Anal. calc. for $C_{20}H_{31}N_3O_3$ (361.48): C 66.45, H 8.64, N 11.63; found: C 66.32, H 8.71, N 11.44.

From the aq. HCl soln. (extraction), 207 mg (23%) of *rac*-**11k** were recovered by filtration.

N^2-[(R)-N^2-Acetyl-2-cyclopropylalanyl]-L-phenylalanine Dimethylamide (**19l**) *and (S,S)-Isomer* **20l**. From *rac*-**11l** (300 mg, 1.8 mmol) in CH_2Cl_2 (10 ml) and **15** according to *Method G*. The residue was chromatographed with Et_2O/i-PrOH 4:1 to yield first 108 mg (31%) of **19l**. M.p. 159.1–159.2°. R_f (Et_2O/i-PrOH 4:1) 0.3. $[\alpha]_D = +33.5$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3390*m*, 3300*s*, 3030*w*, 2965*w*, 2940*m*, 1675*s*, 1660*s*, 1640*s*, 1540*s*, 1505*s*, 1410*m*, 1370*m*, 1295*m*, 1150*m*, 1100*w*, 735*w*, 700*s*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.35–7.1 (*m*, 1 NH, 5 arom. H); 6.9 (br. *s*, 1 NH); 5.25–5.0 (*m*, *ABX*, H–C(2.2)); 3.25–2.8 (*m*, *ABX*, 2 H–C(3.2)); 2.86, 2.62 (2*s*, Me_2N); 1.97 (*s*, Ac); 1.55–1.2 (*m*, $(CH_2)_2CH$); 1.30 (*s*, 1 Me–C(2.1)); 0.6–0.35 (*m*, $(CH_2)_2CH$). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.2, 170.5, 169.3 (3*s*, 3 CO); 136.0, 129.3, 128.0, 126.6 (6 arom. C); 59.5 (*s*, C(2.1)); 50.5 (*d*, C(2.2)); 39.4 (*t*, C(3.2)); 36.6, 35.4 (2*q*, Me_2N); 23.6, 18.8 (2*q*, *Me*–C(2.1), *Me*CO); 18.2 (*d*, $(CH_2)_2CH$); 2.2, 1.4 (2*t*, $(CH_2)_2CH$). MS: 345 (1, M^+), 300 (2), 273 (2), 219 (6), 177 (9), 154 (16), 126 (95), 120 (47), 109 (9), 91 (14), 84 (100), 72 (27), 43 (23). Anal. calc. for $C_{19}H_{27}N_3O_3$ (345.44): C 66.05, H 7.88, N 12.17; found: C 66.00, H 7.70, N 12.40.

Further elution yielded 75 mg (22%) of **20l**. M.p. 196°. R_f (Et_2O/i-PrOH 4:1) 0.24 (tailing). $[\alpha]_D = +37.0$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3360*m*, 3270*s*, 3025*s*, 2940*m*, 1670*s*, 1660*s*, 1640*s*, 1535*s*, 1500*s*, 1420*m*, 1400*m*, 1370*m*, 1290*m*, 1140*m*, 1100*m*, 735*m*, 700*s*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.35–7.1 (*m*, 1 NH, 5 arom. H); 6.86 (br. *s*, 1 NH); 5.25–5.0 (*m*, *ABX*, H–C(2.2)); 3.25–2.8 (*m*, *ABX*, 2 H–C(3.2)); 2.83, 2.68 (2*s*, Me_2N); 1.94 (*s*, Ac); 1.55–1.2 (*m*, $(CH_2)_2CH$); 1.24 (*s*, *Me*–C(2.1)); 0.6–0.35 (*m*, 1 $(CH_2)_2CH$). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.2, 170.5, 169.3 (3*s*, 3 CO); 136.0, 129.3, 128.0, 126.6 (6 arom. C); 59.5 (*s*, C(2.1)); 50.4 (*d*, C(2.2)); 39.3 (*t*, C(3.2)); 36.7, 35.4 (2*q*, Me_2N); 23.6, 18.8 (2*q*, *Me*–C(2.1), *Me*CO); 18.1 (*d*, $(CH_2)_2CH$); 2.2, 1.4 (2*t*, $(CH_2)_2CH$). MS 345 (1, M^+), 300 (1), 273 (2), 219 (5), 176 (11), 154 (14), 126 (94), 120 (50), 101 (8), 91 (17), 84 (100), 72 (34), 42 (29). Anal. calc. for $C_{19}H_{27}N_3O_3$ (345.44): C 66.06, H 7.88, N 12.17; found: C 66.02, H 8.01, N 12.12.

N^2-[(R)-N^2-Acetyl-2-methylvalyl]-L-phenylalanine Dimethylamide (**19m**) *and (S,S)-Isomer* **20m**. From *rac*-**11m** (400 mg, 2.31 mmol) in CH_2Cl_2 (5 ml) and **15** according to *Method G* (45 h at r.t.). The residue was suspended in Et_2O (5 ml), stirred for 1 h, and filtered and the filtrate evaporated: 190 mg (25%) of epimeric imidazolones (which will described later). The Et_2O-insoluble residue was crystallized from CH_2Cl_2: 205 mg (15%) of **19m**. M.p. 211.2–212.2°. R_f (Et_2O/i-PrOH 4:1) 0.40 (tailing). $[\alpha]_D = +12.6$ (EtOH, $c = 0.98$). IR (KBr): 3395*s*, 3300*s*, 3035*w*, 2975*m*, 2945*m*, 1675*s*, 1660*s*, 1640*s*, 1540*s*, 1500*s*, 1410*m*, 1370*m*, 1270*m*, 1185*m*, 1145*m*, 1100*m*, 710*s*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.4–7.05 (*m*, 1 NH, 5 arom. H); 6.23 (br. *s*, 1 NH); 5.25–4.95 (*m*, *ABX*, H–C(2.2)); 3.3–2.75 (*m*, *ABX*, H–C(3.2)); 2.87, 2.61 (2*s*, Me_2N); 2.37 (*sept.*, $J = 6.6$, H–C(3.1)); 1.97 (*s*, Ac); 1.52 (*s*, Me–C(2.1)); 0.92, 0.86 (2*d*, $J = 6.6$, 2 Me–C(3.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.4, 170.8, 169.6 (3*s*, 3 CO); 136.2, 129.2, 128.2, 126.7 (6 arom. C); 63.4 (*s*, C(2.1)); 50.6 (*d*, C(2.2)); 39.6 (*t*, C(3.2)); 36.7, 35.4 (2*q*, Me_2N); 34.1 (*s*, C(3.1)); 24.1 (*q*, *Me*–C(2.1)); 17.9 (*s*, Ac); 17.2 ('*q*', 2 *Me*–C(3.1)). MS: 347 (8, M^+), 304 (11), 286 (22), 262 (13), 219 (13), 189 (30), 177 (33), 156 (33), 128 (76), 120 (60), 91 (12), 86 (100), 72 (35), 69 (17), 46 (44), 43 (33). Anal. calc. for $C_{19}H_{29}N_3O_3$ (347.45): C 65.68, H 8.41, N 12.10; found: C 65.45, H 8.35, N 12.12.

The filtrate was evaporated and chromatographed (SiO_2 (20 g), Et_2O/i-PrOH 4:1): 44.1 mg (11%) of **20m**. Anal. pure material was obtained by further purification with HPLC (*Lichrosorb Si 60*, Et_2O/EtOH 98.5:1.5). R_f (Et_2O/i-PrOH, 4:1) 0.29 (tailing). $[\alpha]_D = +34.5$ ($CHCl_3$, $c = 1.1$). IR (KBr): 3390*s*, 3305*s*, 3040*w*, 3000*w*, 2960*m*, 2940*m*, 1675*m*, 1660*s*, 1640*s*, 1530*s*, 1500*s*, 1405*s*, 1370*m*, 1285*m*, 1185*w*, 1105*m*, 710*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.35–7.1 (*m*, 1 NH, 5 arom. H); 6.08 (br. *s*, 1 NH); 5.25–4.95 (*m*, *ABX*, H–C(2.2)); 3.3–2.8 (*m*, *ABX*, 2 H–C(3.2)); 2.87, 2.68 (2*s*, Me_2N); 2.37 (*sept.*, $J = 6.6$, H–C(3.1)); 2.0 (*s*, Ac); 1.48 (*s*, Me–C(2.1)); 0.94, 0.82 (2*d*, $J = 6.6$, 2 Me–C(3.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.5, 170.8, 169.8 (3*s*, 3 CO); 136.2, 129.2, 128.2, 126.7 (6 arom. C); 63.5 (*s*, C(2.1)); 50.5 (*d*, C(2.2)); 39.4 (*t*, C(3.2)); 36.7, 35.5 (2*q*, Me_2N); 33.9 (*d*, C(3.1)); 24.1 (*q*, *Me*–C(2.1)); 17.5 (*q*, Ac); 17.2 (*q*, 2 *Me*–C(3.1)). MS: 347 (4, M^+), 304 (3), 274 (100), 189 (27), 175 (11), 161 (29), 148 (14), 128 (30), 120 (28), 105 (11), 91 (15), 86 (42), 72 (14), 57 (35), 43 (33). Anal. calc. for $C_{19}H_{29}N_3O_3$ (347.45): C 65.68, H 8.41, N 12.10; found: C 65.47, H 8.30, N 11.87.

N^2-[(R)-N^2-Benzoyl-2-methylphenylalanyl]-L-phenylalanine Dimethylamide (**19p**) *and (S,S)-Isomer* **20p**. A mixture of *rac*-**10p** (974 mg, 3.6 mmol), **15** (785 mg, 3.6 mmol; as the free amine), and TsOH (20 mg) in MeCN (20 ml) was stirred at 60° under Ar for 6 h, cooled to r.t., worked up and purified following *Method H*. The residue was chromatographed (SiO_2 (200 g), Et_2O/i-PrOH 99:1): 731 mg (40%) of **19p**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.23. $[\alpha]_D = +7.0$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3360*m*, 3060*w*, 3020*w*, 2970*w*, 1635*s*, 1620*s*, 1505*m*,

1480*m*, 1450*m*, 1340*w*, 1285*w*, 877*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.8–7.0 (*m*, 1 NH, 15 arom. H); 6.9–6.65 (br. *d*, 1 NH); 5.05–4.85 ('*q*', H–C(2.2)); 3.66, 3.25 (*ca.* 2*d*, *AB*, J_{AB} = 13.0, 2 H–C(3.1)); 3.6–3.25 (*m*, 3 H); 3.15–2.95 ('*t*', H–C(2.2)); 2.75–2.55 (*m*, 1 H); 1.9–1.5 (*m*, 4 H); 1.74 (*s*, Me–C(2.1)). MS: 483 (5, M^+), 395 (5), 392 (17), 266 (11), 238 (24), 120 (16), 105 (100), 91 (14), 77 (29), 72 (20), 55 (10).

Further elution yielded 696 mg (39%) of **20p**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.16. $[\alpha]_D$ = +1.7 ($CHCl_3$, *c* = 1.7). IR (KBr): 3370*m*, 3060*w*, 3030*w*, 2980*w*, 1670*s*, 1630*s*, 1512*m*, 1485*m*, 1455*m*, 1342*w*, 1230*w*, 870*w*, 745*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.75–7.6, 7.5–7.0 (2*m*, 2 NH, 15 arom. H); 5.0–4.85 ('*q*', H–C(2.2)); 3.65, 3.33 (*ca.* 2*d*, *AB*, J_{AB} = 14.0, 2 H–C(3.1)); 3.5–3.2 (*m*, 3 H); 3.15–2.95 ('*t*', 2 H–C(3.2)); 2.65–2.45 (*m*, 1 H); 1.85–1.45 (*m*, 4 H); 1.75 (*s*, Me–C(2.1)). MS: 483 (6, M^+), 392 (11), 266 (15), 238 (33), 120 (15), 105 (100), 91 (15), 77 (15), 55 (12).

N^2-*[(*R*)-N^2-Acetylvalyl]-*L*-phenylalanine Dimethylamide* (**19q**) *and (*S,S*)-Isomer* **20q**. From *rac*-**13** (= *rac*-**11q**; *Chemalog*; 3.77 mol) in THF (3 ml) and **15** according to *Method G* (5 h, r.t.). The residue was chromatographed (SiO_2 (100 g), Et_2O/i-PrOH 4:1): 326 mg (41%) of **19q**. M.p. 138.8–139.9°. R_f (Et_2O/i-PrOH 4:1) 0.46. $[\alpha]_D$ = −4.3 ($CHCl_3$, *c* = 1.0). IR (KBr): 3540*m*, 3460*m*, 3300*s*, 3080*m*, 2970*m*, 2940*m*, 1670*s*, 1650*s*, 1635*s*, 1550*s*, 1500*m*, 1420*m*, 1400*m*, 1375*m*, 1270*m*, 1095*w*, 760*m*, 715*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.44 (br. *d*, *J* = 8.3, 1 NH); 7.3–7.15 (*m*, 5 arom. H); 6.56 (br. *d*, *J* = 9.0, 1 NH); 5.2–5.1 ('*q*', H–C(2.2)); 4.48, 4.45 (2*d*, *J* = 9.0, H–C(2.1)); 3.0 ('*d*', 2 H–C(3.2)); 2.89, 2.66 (2*s*, Me_2N); 2.1–2.05 (*m*, H–C(3.1)); 2.02 (*s*, Ac); 0.92, 0.90 (2*d*, *J* = 6.8, 2 Me–C(3.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 171.9, 170.7, 169.8 (3*s*, 3 CO); 136.0, 129.5, 129.0, 128.0, 126.5 (6 arom. C); 57.8, 50.0 (2*d*, C(2.1), C(2.2)); 39.3 (*t*, C(3.2)); 36.7, 35.5 (2*q*, Me_2N); 31.2 (*d*, C(3.1)); 22.8 (*q*, *Me*CO); 19.1, 18.0 (2*q*, 2 *Me*–C(3.1)). MS: 333 (< 1, M^+), 261 (2), 219 (4), 175 (17), 142 (16), 120 (100), 114 (34), 101 (22), 91 (12), 72 (60), 55 (12), 43 (15). Anal. calc. for $C_{18}H_{27}N_3O_3$ (333.43): C 64.84, H 8.16, N 12.61; found: C 64.53, H 7.91, N 12.54.

Further elution yielded 294 mg (39%) of **20q**. M.p. 151.1–151.7°. R_f (Et_2O/i-PrOH 4:1) 0.33. $[\alpha]_D$ = +50.1 ($CHCl_3$, *c* = 1.0). IR (KBr): 3310*s*, 3070*w*, 2960*w*, 2940*w*, 1670*s*, 1650*s*, 1640*s*, 1540*s*, 1500*m*, 1410*m*, 1370*w*, 1300*w*, 1265*w*, 1150*w*, 1090*w*, 705*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.61 (br. *d*, *J* = 8.2, 1 NH); 7.3–7.2 (*m*, 5 arom. H); 6.67 (br. *d*, *J* = 8.8, 1 NH); 6.75–6.6 ('*q*', H–C(2.2)); 4.49, 4.46 (2*d*, H–C(2.1)); 3.05–3.0 ('*d*', 2 H–C(3.2)); 2.88, 2.71 (2*s*, Me_2N); 2.15–1.85 (*m*, H–C(3.1)); 2.0 (*s*, Ac); 0.87, 0.82 (2*d*, *J* = 6.6, 2 *Me*–C(3.1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 170.9, 170.8, 169.6 (3*s*, 3 CO); 136.2, 129.0, 128.0, 126.5 (6 arom. C); 57.6, 50.0, (2*d*, (C(2.1), C(2.2)); 39.3 (*t*, C(3.2)); 36.7, 35.5 (2*q*, Me_2N); 31.3 (*d*, C(3.1)); 22.8 (*q*, *Me*CO); 19.0, 17.7 (2*q*, 2 Me–C(3.1)). MS: 333 (2, M^+), 261 (3), 219 (4), 175 (12), 142 (11), 120 (100), 114 (33), 101 (24), 91 (10), 72 (87), 55 (14), 43 (21). Anal. calc. for $C_{18}H_{27}N_3O_3$ (333.43): C 64.84, H 8.16, N 12.61; found: C 65.04, H 8.24, N 12.74.

N^2-*[(*R*)-N^2-(Phenylacetyl)phenylalanyl]-*L*-phenylalanine Dimethylamide* (**19r**) and *(*S,S*)-Isomer* **20r**. To a mixture of *rac*-**14** (= *rac*-**11r**; *Bachem*; 2.0 g, 7.06 mmol) in CH_2Cl_2 (30 ml) was added DCC (1.50 g, 7.27 mmol) in small portions at r.t. The mixture was stirred for 30 min at r.t., a soln. of **15** (1.36 g, 7.06 mmol; as free amine) in CH_2Cl_2 (5 ml) was added, and the mixture stirred for 12 h at r.t, filtered, washed with CH_2Cl_2 (2 × 5 ml), and poured onto ice (10 g), 2N aq. HCl (20 ml), and CH_2Cl_2 (50 ml). The org. phase was extracted with sat. aq. $NaHCO_3$ soln. (40 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (300 g), Et_2O/i-PrOH 98:2) and recrystallized from Et_2O: 1.29 g (37%) of **19r**. M.p. 172.1–172.8°. R_f (Et_2O/i-PrOH 98:2) 0.27. $[\alpha]_D$ = +10.2 ($CHCl_3$, *c* = 1.2). IR (KBr): 3320*w*, 3270*m*, 3060*w*, 2920*w*, 1640*s*, 1560*m*, 1492*m*, 1452*w*, 1148*w*, 740*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.45–6.9 (*m*, 15 arom. H); 6.78, 5.88 (2 br. *d*, *J* = 8.0, 2 NH); 5.1–4.95, 4.75–4.65 (*ca.* 2*q*, H–C(2.1), H–C(2.2)); 3.56 (*s*, PhCH_2CO); 3.0–2.85 (*ca.* 2*d*, 2 H–C(3.1), 2 H–C(3.2)); 2.85, 2.58 (2*s*, Me_2N). MS: 457 (3, M^+), 266 (19), 238 (16), 175 (10), 131 (11), 120 (100), 119 (11), 91 (47), 46 (71). Anal. calc. for $C_{28}H_{31}N_3O_3$ (457.58): C 73.50, H 6.83, N 9.18; found: C 73.75, H 6.54, N 9.39.

Further elution yielded, after recrystallization from Et_2O/hexane (−20°), 1.25 g (36%) of **20r**. M.p. 152.0–152.2°. R_f (Et_2O/i-PrOH 98:2) 0.15. $[\alpha]_D$ = +17.6 ($CHCl_3$, *c* = 1.1). IR (KBr): 3430*w*, 3280*m*, 3060*w*, 2920*w*, 1642*s*, 1535*m*, 1495*w*, 1452*w*, 1400*w*, 755*w*, 702*m*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.4–6.95 (*m*, 15 arom. H); 6.80, 6.05 (2 br. *d*, *J* = 8.0, 2 NH); 5.1–4.95, 4.75–4.65 (*ca.* 2*q*, H–C(2.1), H–C(2.2)); 3.05–2.7 (*m*, 2 H–C(3.1), 2 H–C(3.2)); 2.83, 2.56 (2*s*, Me_2N). MS: 457 (2, M^+), 266 (10), 121 (10), 120 (100), 92 (13), 91 (91), 72 (18), 65 (21), 57 (11), 46 (15). Anal. calc. for $C_{28}H_{31}N_3O_3$ (457.58): C 73.50, H 6.83, N 9.18; found: C 73.32, H 6.81, N 9.24.

$N^{2,2}$-*[(*R*)-2-Benzamido-1,2,3,4-tetrahydronaphthalene-2-carbonyl]*-*L*-*phenylalanyl*-*L*-*phenylalanine* $N^{1,3}N^{1,3}$-*(Tetramethylene)amide* (**21a**) *and (*S,S,S*)-Isomer* **22a**. From *rac*-**11a** (6.58 g, 23.7 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (1 kg), Et_2O/i-PrOH 95:5): 7.44 g (48%) of **21a**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 116–117°. R_f (Et_2O/i-PrOH 92:8) 0.38. $[\alpha]_D$ = +7.0 (MeOH, *c* = 1.0). IR (KBr): 3309*m* (br.), 3061*w*, 3025*w*, 2958*w* (br.), 1643*s* (br.), 1528*s*, 1491*s*, 1451*s*, 1294*w*, 743*w*, 699*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.65–7.35 (*m*, 5 arom. H); 7.3–6.95 (*m*, 14 arom. H, 2 NH); 6.25 (*s*, 1 NH); 4.9–4.65 (*m*, H–C(2.2), H–C(2.3)); 3.45–2.65 (*m*, 12 aliph. H); 2.6–2.5 (*m*, 1 aliph. H); 2.2–2.0

(*m*, 1 aliph. H); 1.8–1.45 (*m*, 4 aliph. H). FAB-MS: 643 (35, $[M + H]^+$), 425 (8), 278 (19), 250 (34), 219 (30), 146 (12), 120 (80), 105 (100). Anal. calc. for $C_{42}H_{42}N_4O_4$ (642.80): C 74.74, H 6.59, N 8.72; found: C 74.82, H 6.51, N 8.68.

Further elution yielded 6.7 g (44%) of **22a**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 194.5°. R_f (Et_2O/i-PrOH 92:8) 0.31. $[\alpha]_D = -14.2$ (MeOH, $c = 1.0$). IR (KBr): 3469*m*, 3364*m* (br.), 2966*w*, 1655*s* (br.), 1517*s*, 1450*s*, 1285*w* (br.), 750*m*, 703*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.65–7.35 (*m*, 5 arom. H); 7.3–6.95 (*m*, 14 arom. H, 2 NH); 6.27 (*s*, 1 NH); 4.9–4.7 (*m*, H–C(2.2), H–C(2.3)); 3.45–2.6 (*m*, 13 aliph. H); 2.25–2.0 (*m*, 1 aliph. H); 1.85–1.45 (*m*, 4 aliph. H). FAB-MS: 643 (24, $[M + H]^+$), 425 (8), 278 (26), 250 (32), 219 (28), 146 (13), 120 (75), 105 (100).

$N^{2,2}$-[(R)-2-Benzamido-1,2,3,4-tetrahydro-5-methoxynaphthalene-2-carbonyl]-L-phenylalanyl-L-phenylalanine $N^{1,3}$,$N^{1,3}$-(Tetramethylene)amide (**21b**) *and (S,S,S)-Isomer* **22b**). From *rac*-**11b** (10.0 g, 30.7 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (1.5 kg), Et_2O/i-PrOH 95:5→92:8): 9.1 g (44%) of **21b**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 116–120°. R_f (Et_2O/i-PrOH 92:8) 0.40. $[\alpha]_D = -2.0$ ($CHCl_3$, $c = 0.2$). IR (KBr): 3321*w* (br.), 3027*w*, 2949*w*, 2877*w*, 1644*s* (br.), 1586*w*, 1525*m*, 1488*m*, 1451*m*, 1287*w* (br.), 1259*m*, 1100*w*, 1076*w*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.31 (br. *s*, 1 NH); 8.25 (*d*, $J = 9.1$, 1 NH); 7.85–7.75 (*m*, 2 arom. H); 7.67 (*d*, $J = 9.1$, 1 NH); 7.6–7.35 (*m*, 3 arom. H); 7.35–7.0 (*m*, 11 arom. H); 6.73, 6.63 (2*d*, $J = 7.6$, 2 arom. H); 4.7–4.45 (*m*, H–C(2.2), H–C(2.3)); 3.73 (*s*, MeO); 3.45–2.7 (*m*, *ca.* 11 aliph. H); 2.6–2.25 (*m*, 4 aliph. H); 1.95–1.45 (*m*, 6 aliph. H). FAB-MS: 311 (55, $[M + H]^+$), 455 (40), 280 (50), 219 (38), 120 (95), 105 (100).

Further elution yielded 8.9 g (43%) of **22b**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 182–184°. R_f (Et_2O/i-PrOH 92:8) 0.29. $[\alpha]_D = -20.0$ ($CHCl_3$, $c = 0.2$). IR (KBr): 3413*w*, 3327*w* (br.), 3061*w*, 3028*w*, 2929*w*, 1650*s*, 1642*s*, 1467*m*, 1452*m*, 1289*w* (br.), 1258*m*, 1089*w*, 1076*w*, 701*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.32 (*d*, $J = 7.6$, 1 NH); 8.31 (br. *s*, 1 NH); 7.85–7.7 (*m*, 2 arom. H); 7.60 (*d*, $J = 7.6$, 1 NH); 7.6–7.35 (*m*, 4 arom. H); 7.3–6.9 (*m*, 12 arom. H); 6.74, 6.62 (2*d*, $J = 7.6$, 2 arom. H); 4.7–4.45 (*m*, H–C(2.2), H–C(2.3)); 3.37 (*s*, MeO); 3.45–2.7 (*m*, 10 aliph. H); 2.6–2.3 (*m*, 4 aliph. H); 2.0–1.45 (*m*, 6 aliph. H). FAB-MS: 673 (30, $[M + H]^+$), 455 (10), 308 (28), 280 (53), 219 (40), 120 (92), 105 (100).

$N^{2,2}$-[(R)-2-Benzamido-1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carbonyl]-L-phenylalanyl-L-phenylalanine $N^{1,3}$,$N^{1,3}$-(Tetramethylene)amide (**21c**) *and (S,S,S)-Isomer* **22c**. From *rac*-**11c** (5.0 g, 15.38 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (750 g), Et_2O/i-PrOH 95:5→92:8): 4.45 g (43%) of **21c**. Amorphous solid. Crystallization from AcOEt/hexane gave 4.19 g (40.5%) of **21c**. M.p. 113–115°. R_f (Et_2O/i-PrOH 92:8) 0.38. $[\alpha]_D = -2.0$ (EtOH, $c = 0.4$). IR (KBr): 3408*w* (br.), 3325*w*, 3060*w*, 3027*w*, 2930*w*, 1643*s* (br.), 1579*w*, 1528*m*, 1503*s*, 1451*m*, 1341*w*, 1292*w*, 1269*w*, 1237*w*, 1156*w*, 1035*w*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 8.30 (br. *s*, 1 NH); 8.25 (*d*, $J = 7.6$, 1 NH); 7.85–7.75 (*m*, 2 arom. H); 7.62 (*d*, $J = 8.3$, 1 NH); 7.55–7.5 (*m*, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.3–7.15 (*m*, 5 arom. H); 7.15–7.0 (*m*, 5 arom. H); 6.91 (*d*, $J = 8.5$, 1 arom. H); 6.7–6.65 (*m*, 1 arom. H); 6.6–6.55 (*m*, 1 arom. H); 4.65–4.5 (*m*, H–C(2.2), H–C(2.3)); 3.68 (*s*, MeO); 3.4–3.3 (*m*, 1 aliph. H); 3.3–3.2 (*m*, 1 aliph. H); 3.2–3.1 (*m*, 1 aliph. H); 3.1–2.7 (*m*, 7 aliph. H); 2.65–2.35 (*m*, 3 aliph. H); 1.9–1.8 (*m*, 1 aliph. H); 1.75–1.55 (*m*, 4 aliph. H). FAB-MS: 673 (25, $[M + H]^+$), 308 (15), 280 (20), 219 (25), 187 (22), 120 (52), 105 (100).

Further elution yielded 4.35 g (42%) of **22c**. Amorphous solid. R_f (Et_2O/i-PrOH 92:8) 0.30. $[\alpha]_D = -18.0$ (EtOH, $c = 0.5$). IR (KBr): 3413*w* (br.), 3314*w* (br.), 3060*w*, 3027*w*, 2950*w*, 2876*w*, 1643*s* (br.), 1579*w*, 1525*m* (br.), 1503*s*, 1454*s*, 1340*w*, 1291*w*, 1270*w*, 1236*w*, 1034*w*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 8.30 (br. *s*, 1 NH); 8.29 (*d*, $J = 5.4$, 1 NH); 7.85–7.7 (*m*, 2 arom. H); 7.57 (*d*, $J = 8.2$, 1 NH); 7.55–7.35 (*m*, 4 arom. H); 7.35–7.0 (*m*, 10 arom. H); 6.90 (*d*, $J = 8.4$, 1 arom. H); 6.75–6.65 (*m*, 1 arom. H); 6.65–6.5 (*m*, 1 arom. H); 4.7–4.5 (*m*, H–C(2.2), H–C(2.3)); 3.69 (*s*, MeO); 3.45–3.1 (3*m*, 3 aliph. H); 3.1–2.75 (2*m*, 7 aliph. H); 2.75–2.3 (*m*, 3 aliph. H); 2.0–1.85 (*m*, 1 aliph. H); 1.75–1.5 (*m*, 4 aliph. H). FAB-MS: 673 (15, $[M + H]^+$), 308 (12), 280 (20), 219 (20), 187 (18), 120 (40), 105 (100).

$N^{2,2}$-[(R)-2-Benzamido-1,2,3,4-tetrahydro-7-methoxynaphthalene-2-carbonyl]-L-phenylalanyl-L-phenylalanine $N^{1,3}$,$N^{1,3}$-(Tetramethylene)amide (**21d**) *and (S,S,S)-Isomer* **22d**. From *rac*-**11d** (10.0 g, 30.73 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (1.2 kg), Et_2O/i-PrOH 95:5→92:8): 9.0 g (43.5%) of **21d**. Amorphous solid. A sample was crystallized from AcOEt/hexane. M.p. 109–110°. R_f (Et_2O/i-PrOH 92:8) 0.35. $[\alpha]_D = -27.0$ (MeOH, $c = 0.5$). IR (KBr): 3410*w* (br.), 3317*w* (br.), 3060*w*, 3027*w*, 2950*w*, 2876*w*, 1644*s* (br.), 1579*w*, 1563*s*, 1451*m*, 1343*w*, 1292*w*, 1267*w*, 1158*w*, 1033*w*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.36 (br. *s*, 1 NH); 8.23 (*d*, $J = 7.6$, 1 NH); 7.9–7.8 (*m*, 2 arom. H); 7.67 (*d*, $J = 7.6$, 1 NH); 7.6–7.35 (*m*, 3 arom. H); 7.3–7.05 (*m*, 10 arom. H); 6.90 (*d*, $J = 7.9$, 1 arom. H); 6.7–6.5 (*m*, 2 arom. H); 4.65–4.5 (*m*, H–C(2.2), H–C(2.3)); 3.68 (*s*, MeO); 3.45–2.65 (*m*, 11 aliph. H); 2.6–2.2 (*m*, 4 aliph. H); 1.9–1.45 (*m*, 5 aliph. H). FAB-MS: 673 (40, $[M + H]^+$), 217 (95), 109 (35), 91 (100).

Further elution yielded 9.1 g (44%) of **22d**. Amorphous solid. A sample was crystallized from EtOH/H_2O, which gave suitable crystals for X-ray analysis. M.p. 127–129°. R_f (Et_2O/i-PrOH 92:8) 0.28. $[\alpha]_D = +0.8$ (EtOH, $c = 0.5$). IR (KBr): 3472*m*, 3364*m*, 3214*w* (br.), 3060*w*, 3026*w*, 2967*w*, 2867*w*, 1670*s*, 1640*s* (br.), 1504*s*, 1451*m*, 1319*w*, 1287*w*, 1244*w*, 1220*w*, 1191*w*, 1029*w*, 872*w*, 697*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.35 (br. *s*, 1 NH); 8.32 (*d*, $J = 7.4$, 1 NH); 7.85–7.75 (*m*, 2 arom. H); 7.58 (*d*, $J = 7.9$, 1 NH); 7.55–7.4 (*m*, 3 arom. H); 7.35–7.15 (*m*, 5 arom. H); 7.09 (*s*, 5 arom. H); 6.97 (*d*, $J = 7.9$, 1 arom. H); 6.75–6.65 (*m*, 1 arom. H); 6.6–6.5 (*m*, 1 arom. H); 4.65–4.5 (*m*, H–C(2.2), H–C(2.3)); 3.70 (*s*, MeO); 3.45–2.75 (*m*, *ca.* 10 aliph. H); 2.65–2.3 (*m*, 4 aliph. H); 2.0–1.8 (*m*, 1 aliph. H); 1.75–1.5 (*m*, 4 aliph. H). FAB-MS: 673 (90, $[M + H]^+$), 280 (40), 219 (30), 120 (50), 105 (100).

$N^{2,2}$-*[(*R*)-2-Benzamido-1,2,3,4-tetrahydro-8-methoxynaphthalene-2-carbonyl]*-L-*phenylalanyl*-L-*phenylalanine* $N^{1,3}$,$N^{1,3}$-*(Tetramethylene)amide* (**21e**) *and (*S,S,S*)-Isomer* **22e**. From *rac*-**11e** (10.0 g, 30.73 mmol) and **18** according to *Method H*. The residue was suspended in AcOEt/hexane 4:1, stirred for 1 h, filtered, washed with AcOEt/hexane 4:1, and dried under reduced pressure: 8.06 g (39%) of pure **21e**. The filtrate was evaporated and the residue chromatographed (SiO_2 (800 g), Et_2O/i-PrOH 95:5→92:8): 0.93 g (4.5%) of **21e**, in total 8.99 g (43.5%) of **21e**. M.p. 134–136°. R_f (Et_2O/i-PrOH 92:8) 0.40. $[\alpha]_D = -57.8$ ($CHCl_3$, $c = 0.5$). IR (KBr): 3412*w* (br.), 3335*w* (br.), 3061*w*, 2929*w*, 2879*w*, 1645*s* (br.), 1584*s*, 1521*s* (br.), 1470*s*, 1452*s*, 1526*m*, 1103*w*, 1076*w*, 701*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.42 (br. *s*, 1 NH); 8.24 (*d*, $J = 7.5$, 1 NH); 7.9–7.85 (*m*, arom. H); 7.68 (*d*, $J = 7.5$, 1 NH); 7.6–7.4 (*m*, 3 arom. H); 7.35–7.0 (*m*, 11 arom. H); 6.75–6.7 (*m*, 1 arom. H); 6.65–6.55 (*m*, 1 arom. H); 4.65–4.51 (*m*, H–C(2.2), H–C(2.3)); 3.74 (*s*, MeO); 3.45–2.7 (*m*, 10 aliph. H); 2.6–2.15 (*m*, 4 aliph. H); 1.9–1.45 (*m*, 6 aliph. H). FAB-MS: 673 (20, $[M + H]^+$), 308 (15), 280 (35), 219 (25), 187 (20), 120 (65), 105 (100).

Further elution yielded 9.30 g (45%) of **22e**. Amorphous solid. R_f (Et_2O/i-PrOH 92:8) 0.35. $[\alpha]_D = +19.0$ ($CHCl_3$, $c = 0.5$). IR (KBr): 3417*w* (br.), 3308*w* (br.), 3060*w*, 3027*w*, 2951*w*, 1876*w*, 1644*s* (br.), 1584*w*, 1526*s* (br.), 1468*s*, 1451*s*, 1341*w*, 1290*w*, 1256*m*, 1100*w*, 776*w*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.41 (br. *s*, 1 NH); 8.27 (*d*, $J = 7.5$, 1 NH); 7.9–7.8 (*m*, 2 arom. H); 7.65 (*d*, $J = 7.5$, 1 NH); 7.6–7.4 (*m*, 3 arom. H); 7.3–7.0 (*m*, 11 arom. H); 6.8–6.7 (*m*, 1 arom. H); 6.7–6.55 (*m*, 1 arom. H); 4.7–4.45 (*m*, H–C(2.2), H–C(2.3)); 3.79 (*s*, MeO); 3.45–2.75 (*m*, 10 aliph. H); 2.7–2.35 (*m*, 4 aliph. H); 2.0–1.8 (*m*, 1 aliph. H); 1.8–1.45 (*m*, 4 aliph. H). FAB-MS: 673 (20, $[M + H]^+$), 308 (15), 280 (25), 219 (28), 187 (15), 120 (40), 105 (100).

$N^{2,2}$-*[(*R*)-2-Benzamido-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carbonyl]*-L-*phenylalanyl*-L-*phenylalanine* $N^{1,3}$,$N^{1,3}$-*(Tetramethylene)amide* (**21f**) *and (*S,S,S*)-Isomer* **22f**. From *rac*-**11f** (5.0 g, 14.07 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (1 kg), Et_2O/i-PrOH 92:8→90:10) and crystallized from AcOEt/hexane: 4.05 g (41%) of **21f**. White solid. M.p. 133.5–135°. R_f (Et_2O/i-PrOH 92:8) 0.20. $[\alpha]_D = -23.0$ (MeOH, $c = 0.1$). IR (KBr): 3405*w* (br.), 3317w (br.), 3060*w*, 3027*w*, 2932*w*, 2876*w*, 1645*s* (br.), 1514*s*, 1450*s*, 1342*w*, 1285*w*, 1255*m*, 1221*m*, 1115*m*, 1030*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.65–7.6 (*m*, 2 arom. H); 7.55–7.5 (*m*, 1 arom. H); 7.45–7.4 (*m*, 2 arom. H); 7.3–7.05 (*m*, 10 arom. H); 7.05 (*d*, $J = 8.1$, 1 NH); 6.98 (*d*, $J = 7.9$, 1 NH); 6.59, 6.57 (2*s*, 2 arom. H); 6.24 (br. *s*, 1 NH); 4.85–4.7 (*m*, H–C(2.2), H–C(2.3)); 3.85, 3.84 (2*s*, 2 MeO); 3.4–3.2 (*m*, 5 aliph. H); 3.15–3.05 (*m*, 1 aliph. H); 3.0–2.5 (*m*, 7 aliph. H); 2.15–2.0 (*m*, 1 aliph. H); 1.8–1.45 (*m*, 4 aliph. H). FAB-MS: 703 (50, $[M + H]^+$), 338 (20), 310 (20), 217 (25), 120 (45), 105 (100).

Further elution yielded 4.01 g (40.5%) of **22f**. Amorphous solid. R_f (Et_2O/i-PrOH 92:8) 0.15. $[\alpha]_D = +13.0$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3409*w* (br.), 3321*w* (br.), 3028*w*, 2931*w*, 2834*w*, 1644*s* (br.), 1514*s*, 1450*m*, 1431*w*, 1285*w*, 1222*m*, 1115*m*, 1029*w*, 851*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.65–7.45 (*m*, 3 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.3–6.95 (*m*, 10 arom. H, 2 NH); 6.57, 6.54 (2*s*, 2 arom. H); 3.86, 3.85 (2*s*, 2 MeO); 3.45–3.2 (*m*, 4 aliph. H); 3.2–2.95 (*m*, 4 aliph. H); 2.95–2.6 (*m*, 5 aliph. H); 2.25–2.05 (*m*, 1 aliph. H); 1.85–1.45 (*m*, 5 aliph. H). FAB-MS: 703 (70, $[M + H]^+$), 640 (35), 184 (50), 120 (50), 105 (100).

$N^{2,2}$-*[(*R*)-1-Benzamido-1,2,3,4-tetrahydronaphthalene-1-carbonyl]*-L-*phenylalanyl*-L-*phenylalanine* $N^{1,3}$,$N^{1,3}$-*(Tetramethylene)amide* (**21g**) *and (*S,S,S*)-Isomer* **22g**. From *rac*-**11g** (5.05 g, 17.1 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (900 g), AcOEt/hexane 4:1→1:0): 5.47 g (47%) of **21g**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 165–166°. R_f (Et_2O/i-PrOH 92:8) 0.51. $[\alpha]_D = +21.4$ (MeOH, $c = 0.5$). IR (KBr): 3408*m*, 3262*w*, 3061*w*, 3027*w*, 2932*w*, 2875*w*, 1738*w*, 1658*s*, 1622*s*, 1474*s* (br.), 1028*w*, 747*m*, 700*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0 (*s*, 1 NH); 7.80 (*d*, $J = 7$, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.3–7.0 (*m*, 2 arom. H); 6.76 (*d*, $J = 7$, 2 arom. H); 6.66 (*d*, $J = 8$, 1 NH); 5.78 (*d*, $J = 8$, 1 NH); 4.85–4.6 (*m*, H–C(2.2), H–C(2.3)); 3.5–3.2 (*m*, 3 aliph. H); 3.1–2.65 (2*m*, 7 aliph. H); 2.6–2.45 (*m*, 1 aliph. H); 2.15–1.85 (2*m*, 2 aliph. H); 1.8–1.4 (*m*, 5 aliph. H). FAB-MS: 643 (16, $[M + H]^+$), 304 (4), 278 (7), 250 (20), 219 (27), 157 (27), 120 (50), 105 (100). Anal. calc. for $C_{40}H_{42}N_4O_4$ (642.80): C 74.74, H 6.59, N 8.72; found: C 74.48, H 6.60, N 8.69.

Further elution yielded 5.25 g (45.1%) of **22g**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 118–120°. R_f (Et_2O/i-PrOH 92:8) 0.28. $[\alpha]_D = -65.5$ (MeOH, $c = 0.5$). IR (KBr): 3415*m*, 3290*m*, 3060*w*, 3026*w*, 2931*w* (br.), 2873*w*, 1645*s* (br.), 1498*s* (br.), 1449*s*, 1030*w*, 747*w*, 700*m*. ^{1}H-NMR ($CDCl_3$,

250 MHz): 7.83 (*d*, *J* = 6, 2 arom. H); 7.55–7.05 (2*m*, 15 arom. H, 2 NH); 7.0–6.9 (*m*, 2 arom. H); 5.64 (*d*, *J* = 8, 1 NH); 4.9–4.75 (*m*, H–C(2.2), or H–C(2.3)); 4.65–4.55 (*m*, H–C(2.3) or H–C(2.2)); 3.5–3.25 (*m*, 3 aliph. H); 3.2–2.45 (*m*, 7 aliph. H); 2.15–2.0 (*m*, 1 aliph. H); 1.9–1.55 (*m*, 5 aliph. H); 1.35–1.1 (*m*, 1 aliph. H). FAB-MS: 643 (19, $[M + H]^+$), 425 (5), 278 (10), 250 (23), 219 (25), 157 (30), 120 (51), 105 (100). Anal. calc. for $C_{40}H_{42}N_4O_4$ (642.80): C 74.74, H 6.59, N 8.72; found: C 74.96, H 6.70, N 8.66.

$N^{2.2}$-*[(*R*)-1-(4-Bromobenzamido)-1,2,3,4-tetrahydronaphthalene-1-carbonyl]*-L-*phenylalanyl*-L-*phenylalanine* $N^{1.3}$,$N^{1.3}$-*(Tetramethylene)amide* (**21g′**) *and (*S,S,S*)-Isomer* **22g′**. From *rac*-**11g′** (0.36 g, 1.01 mmol) and **18** according to *Method H*. The residue was chromatographed (SiO_2 (150 g), Et_2O/i-PrOH 97:3→95:5): 298 mg (41%) of **21g′**. Amorphous solid. A sample was crystallized from MeOH, which gave suitable crystals for X-ray analysis. M.p. 167–167.5°. R_f (Et_2O/i-PrOH 92:8) 0.57. $[\alpha]_D$ = +28.0 (MeOH, *c* = 0.1). IR (KBr): 3405*m* (br.), 3060*w*, 3027*w*, 2930*w*, 2874*w*, 1656*s* (br.), 1497*s* (br.), 1471*s* (br.), 1010*w*, 845*w*, 751*m*, 701*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.03 (*s*, 1 NH); 7.66, 7.54 (2*d*, *J* = 8, 4 arom. H); 7.30–7.0 (*m*, 12 arom. H); 6.8–6.65 (*m*, 2 arom. H, 1 NH); 5.76 (*d*, *J* = 8, 1 NH); 4.85–4.65 (*m*, H–C(2.2), H–C(2.3)); 3.55–3.2 (2*m*, 3 aliph. H); 3.1–2.65 (*m*, 7 aliph. H); 2.6–2.50 (*m*, 1 aliph. H); 2.15–1.9 (2*m*, 2 aliph. H); 1.85–1.50 (*m*, 5 aliph. H). FAB-MS: 721 (12, $[M + H]^+$), 643 (14), 328 (8), 304 (6), 276 (5), 250 (11), 219 (52), 183 (38), 157 (48), 120 (100), 105 (60). Anal. calc. for $C_{40}H_{41}BrN_4O_4$ (721.66): C 66.57, H 5.73, N 7.76; found: C 66.81, H 5.63, N 7.64.

Further elution yielded 318 mg (43.5%) of **22g′**. Amorphous solid. A small sample was crystallized from AcOEt/hexane. M.p. 155–156°. R_f (Et_2O/i-PrOH 92:8) 0.36. $[\alpha]_D$ = −60.0 (MeOH, *c* = 0.1). IR (KBr): 3407*m*, 3306*m*, 3061*w*, 3027*w*, 2948*w*, 2873*w*, 1645*s*, 1499*s*, 1450*s*, 1010*w*, 752*m*, 701*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.72, 7.52 (2*d*, *J* = 8, 4 arom. H); 7.35 (*d*, *J* = 8, 1 arom. H); 7.3–7.1 (*m*, 12 arom. H); 7.0 (*d*, *J* = 8, 1 NH); 6.95–6.85 (*m*, 2 arom. H); 5.57 (*d*, *J* = 8, 1 NH); 4.85 (*m*, H–C(2.2) or H–C(2.3)); 4.65–4.5 (*m*, H–C(2.3) or H–C(2.2)); 3.5–3.25 (*m*, 3 aliph. H); 3.14, 3.09 (2*d*, *J* = 5., 1 aliph. H); 3.0–2.45 (*m*, 7 aliph. H); 2.1–2.0 (*m*, 1 aliph. H); 1.9–1.55 (*m*, 6 aliph. H). FAB-MS: 721 (13, $[M + H]^+$), 643 (21), 328 (10), 304 (8), 276 (7), 250 (16), 219 (43), 183 (37), 157 (50), 120 (100), 105 (73). Anal. calc. for $C_{40}H_{41}BrN_4O_4$ (721.66): C 66.57, H 5.73, N 7.76; found: C 66.55, H 5.76, N 7.76.

$N^{2.2}$-*[(*R*)-1-Benzamido-2,3-dihydro-6-methoxy-1*H*-indene-1-carbonyl]*-L-*phenylalanyl*-L-*phenylalanine* $N^{1.3}$,$N^{1.3}$-*(Tetramethylene)amide* (**21h**) *and (*S,S,S*)-Isomer* **22h**. From *rac*-**11h** (10.0 g, 32.1 mmol) and **18** according to *Method I*. The residue was chromatographed (SiO_2 (1.5 kg), Et_2O/i-prOH 95:5→92:8) to yield first, after crystallization from AcOEt/hexane, 10.36 g (49%) **21h**. Amorphous solid. M.p. 163–164°. R_f (Et_2O/i-PrOH 92:8) 0.44. $[\alpha]_D$ = +8.6 ($CHCl_3$, *c* = 0.5). IR (KBr): 3416*w*, 3355*w*, 3262*w*, 3060*w*, 3026*w*, 2947*w*, 1680*m*, 1656*s*, 1621*s*, 1580*w*, 1531*m*, 1491*s*, 1452*m*, 1289*m*, 1261*w*, 1181*w*, 1028*w*, 745*w*, 702*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.43 (*d*, *J* = 8.0, 1 NH); 8.0–7.9 (*m*, 2 arom. H); 7.6–7.4 (*m*, 3 arom. H, 1 NH); 7.3–6.9 (*m*, 12 arom. H); 6.85–6.75 (*m*, 1 arom. H); 4.65–4.45 (*m*, H–C(2.2), H–C(2.3)); 3.66 (*s*, 1 MeO); 3.4–3.05 (*m*, 3 aliph. H); 3.05–2.7 (*m*, 8 aliph. H); 2.35–2.15 (*m*, 1 aliph. H); 1.75–1.45 (*m*, 4 aliph. H). FAB-MS: 659 (22, $[M + H]^+$), 266 (28), 219 (35), 174 (30), 120 (60), 105 (100).

Further elution yielded, after recrystallization from AcOEt/hexane, 10.35 g, (49%) of **22h**. M.p. 118–119°. R_f (Et_2O/i-PrOH 92:8) 0.26. $[\alpha]_D$ = −48.0 ($CHCl_3$, *c* = 0.5). IR (KBr): 3404*w* (br.), 3304*w*, 3060*w*, 3022*w*, 2951*w*, 1680*m*, 1643*s* (br.), 1526*m*, 1491*s*, 1450*s*, 1326*w*, 1287*m*, 1215*w*, 1031*w*, 745*w*, 700*m*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.91 (br. *s*, 1 NH); 8.22 (*d*, *J* = 7.6, 1 NH); 8.05–7.95 (*m*, 2 arom. H); 7.72 (*d*, *J* = 7.6, 1 NH); 7.6–7.4 (*m*, 3 arom. H); 7.3–6.95 (*m*, 12 arom. H); 6.9–6.8 (*m*, 1 arom. H); 4.65–4.5, 4.5–4.4 (2*m*, H–C(2.2), H–C(2.3)); 3.69 (*s*, MeO); 3.45–2.75 (*m*, 11 aliph. H); 2.25–2.05 (*m*, 1 aliph. H); 1.8–1.5 (*m*, 4 aliph. H). FAB-MS: 659 (30, $[M + H]^+$), 266 (28), 219 (28), 174 (30), 120 (60), 105 (100).

$N^{2.2}$-*[(*R*)-*$N^{2.1}$*-Benzoyl-2-phenylalanyl]*-L-*phenylalanyl*-L-*phenylalanine Dimethylamide* (**21n**) *and (*S,S,S*)-Isomer* **22n**. A mixture of **10n** (500 mg, 1.99 mmol), **17** (675 mg, 1.99 mmol), and TsOH (20 mg) in MeCN (30 ml) was refluxed under Ar for 48 h, cooled to r.t., worked up, and purified following *Method H*. The residue was chromatographed (SiO_2 (100 g), Et_2O/i-PrOH 99:1): 353 mg (27%) of **21n**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.18. $[\alpha]_D$ = +23.8 ($CHCl_3$, *c* = 0.94). IR (KBr): 3380*w*, 3300*w*, 3060*w*, 3025*w*, 2930*w*, 1640*s*, 1500*s*, 1475*s*, 1452*w*, 1440*w*, 1075*w*, 1027*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 8.10 (br. *s*, 1 NH); 7.95–7.65 (*m*, 2 arom. H); 7.55–6.85 (*m*, 16 arom. H); 6.75–6.55 (*m*, 2 arom. H); 6.02 (br. *d*, 1 NH); 5.15–4.85, 4.85–4.55 (2*m*, H–C(2.2), H–C(2.3)); 3.05–2.65 (*m*, 2 H–C(3.2), 2 H–C(3.3)); 2.82, 2.57 (2*s*, Me_2N); 2.0 (*s*, Me–C(2.1)). MS: 590 (< 1, M^+), 252 (6), 225 (16), 224 (36), 219 (11), 146 (5), 131 (7), 121 (5), 120 (20), 106 (10), 105 (100), 104 (13), 103 (16), 91 (15), 78 (8), 77 (44), 76 (5), 72 (18), 51 (11), 44 (11).

Further elution yielded 494 mg (37%) of **22n**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.10. $[\alpha]_D$ = −4.5 ($CHCl_3$, *c* = 1.0). IR (KBr): 3400*m*, 3300*m*, 3060*w*, 3025*w*, 2930*w*, 1640*s*, 1500*s*, 1480*m*, 1445*w*, 1290*w*, 1030*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.95–7.65, 7.55–6.8 (2*m*, 2 NH, 20 arom. H); 6.03 (br. *d*, *J* = 8.0, 1 NH); 5.15–4.8, 4.75–4.45 (2*m*, H–C(2.2), H–C(2.3)); 3.25–2.65 (*m*, 2 H–C(3.2), 2 H–C(3.3)); 2.80, 2.60 (2*s*, Me_2N);

1.83 (*s*, Me–C(2.1)). MS: 590 (< 1, $M^{+\cdot}$), 299 (8), 272 (8), 252 (12), 225 (7), 224 (27), 149 (9), 131 (11), 121 (8), 120 (47), 105 (100), 104 (16), 103 (20), 91 (29), 77 (39), 57 (12), 51 (14), 46 (25).

$N^{2,2}$-*[(*R*)-*$N^{2,1}$*Benzoyl-2-phenyl-2-allylglycyl]*-L-*phenylalanyl*-L-*phenylalanine Dimethylamide* (**21o**) *and (*S,S,S*)-Isomer* **22o**. A mixture of *rac*-**10o** (246 mg, 0.88 mmol), **17** (300 mg, 0.85 mmol), and TsOH (10 mg), in MeCN (3 ml) was refluxed under Ar for 72 h, cooled to r.t., worked up and purified following *Method H*. The residue was chromatographed (SiO_2 (50 g), Et_2O/i-PrOH 99:1): 235 mg (41%) of **21o**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.22. $[\alpha]_D = +14.1$ ($CHCl_3$, $c = 0.71$). IR (KBr): 3380*w*, 3300*w*, 3060*w*, 3025*w*, 2925*w*, 1640*s*, 1500*s*, 1475*s*, 1420*w*, 1255*w*, 1120*w*, 1030*w*, 925*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.95–7.7, 7.55–6.65 (2*m*, 2 NH, 20 arom. H); 6.53 (br. *d*, $J = 8.0$, 1 NH); 5.95–5.45 (*m*, CH_2=C*H*CH_2); 5.3–4.55 (*m*, CH_2=CHCH_2, H–C(2.2), H–C(2.3)); 3.75–3.35, 3.15–2.75 (2*m*, CH_2=CHCH_2, 2 H–C(3.2), 2 H–C(3.3)); 2.87, 2.58 (2*s*, Me_2N). MS: 616 (< 1, $M^{+\cdot}$), 425 (6), 366 (5), 278 (12), 251 (7), 250 (22), 131 (6), 129 (8), 120 (28), 105 (100), 104 (11), 91 (16), 77 (31), 46 (20).

Further elution yielded 224 mg (39%) of **22o**. Amorphous white solid. R_f (Et_2O/i-PrOH 99:1) 0.16. $[\alpha]_D = -34.8$ ($CHCl_3$, $c = 0.67$). IR (KBr): 3380*w*, 3300*w*, 3060*w*, 3025*w*, 2925*w*, 1640*s*, 1500*s*, 1480*s*, 1420*w*, 1290*w*, 1255*w*, 1120*w*, 1030*w*, 920*w*, 700*m*. ^{1}H-NMR ($CDcl_3$, 90 MHz): 7.95–7.75 (*m*, 3 arom. H); 7.62 (br. *s*, 1 NH); 7.55–6.9 (*m*, 1 NH, 17 arom. H); 6.37 (br. *d*, $J = 7.5$, 1 NH); 5.65–5.2 (*m*, CH_2=C*H*CH_2); 5.2–4.45 (*m*, CH_2=CHCH_2, H–C(2.2), H–C(2.3)); 3.45–2.65 (*m*, CH_2=CHCH_2)); 2.80, 2.63 (2*s*, Me_2N). MS: 616 (< 1, $M^{+\cdot}$), 425 (5), 278 (16), 250 (20), 131 (8), 129 (7), 120 (32), 105 (100), 104 (13), 103 (10), 91 (20), 77 (32), 57 (11), 46 (19).

Compounds 24 and 15–18. – *(*R*)-Methyl 2-{[(*tert*-Butyl)oxycarbonyl]amino}-1,2,3,4-tetrahydronaphthalene-2-carboxylate* (**24**). To a stirred mixture of (*R*)-**1a** (700 mg, 3.07 mmol) in dry MeOH (3 ml) at 0° was added dropwise $SOCl_2$ (0.67 ml, 9 mmol; *Fluka*) followed by 15% HCl in MeOH (3 ml). The mixture was stirred at 0° for 15 min and then heated at 50° for 5.5 h. The soln. was evaporated and the residue dissolved in $CHCl_3$ (100 ml). The org. phase was washed with sat. $NaHCO_3$ soln. (50 ml), dried ($MgSO_4$), and evaporated, and the crude brown liquid **23** used without further purification. To a soln. of the crude material in DMF (10 ml) was added di(*tert*-butyl) dicarbonate (*Fluka*; 737 mg, 3.38 mmol) and stirred at r.t. for 72 h. The DMF was then removed under high vacuum, the residue extracted with AcOEt (100 ml) and ice-cold 0.5N aq. HCl (50 ml), the org. phase washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude purified by flash chromatography on 50 g SiO_2, Hexane/AcOEt 4:1. After drying under high vacuum, 919 mg (98%) of **24** was obtained as a viscous yellow liquid. $[\alpha]_D = -25.0$ ($c = 0.5$, MeOH). IR (KBr): 3367*w*, 2950*m*, 1742*s*, 1714*s*, 1495*s*, 1454*m*, 1366*m*, 1249*s*, 1168*s*, 1064*m*, 745*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.22–7.02 (*m*, 4 arom. H); 4.79 (br. *s*, 1 NH); 3.78 (*s*, 1 MeO); 3.28, 2.95 (2*d*, $J = 16$, 2 aliph. H); 2.90–2.80 (*m*, 2 aliph. H); 2.59–2.46 (*m*, 1 aliph. H); 2.22–2.06 (*m*, 1 aliph. H); 1.41 (*s*, 1 *t*-Bu). MS: 204 (7), 188 (100), 146 (22), 129 (74), 57 (82).

L-*Phenylalanine Dimethylamide* [31] **15**. To a stirred soln. of 8.5 g (28.4 mmol) of Z-(*S*)-Phe in CH_2Cl_2 (100 ml) was added at 0° 5.86 g (28.4 mmol) of DCC in small portions, followed by addition of Me_2NH (gas), until no starting material was observable. The mixture was stirred for 2 h at r.t., filtered, washed with CH_2Cl_2 and the filtrate poured onto ice, 2N aq. HCl soln. (40 ml), the org. layer washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), the solvents were removed and the residue dried under reduced pressure. The the crude residue was added at 0° a cold soln. of 33% HBr soln. in AcOH (150 ml), and the mixture was stirred for 3 h at 0°. The product precipitated by addition of Et_2O (–10 ml). Filtration and drying under reduced pressure gave 7.04 g (90%) of **15** (hydrobromide salt). M.p. 256.3–257.0°. $[\alpha]_D = +56.0$ (H_2O, $c = 1.6$). IR (KBr): 3060*m*, 2940*m*, 2680*m*, 1650*s*, 1555*s*, 1490*w*, 1445*s*, 1395*w*, 1365*w*, 1205*w*, 1155*w*, 1140*m*, 1095*w*, 1035*w*, 765*w*, 700*w*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.23 (*s*, 5 arom. H); 3.90 (*t*, $J = 7.0$, H–C(2)); 2.87, 2.70 (2*s*, Me_2N); 2.85 (*d*, $J = 7.0$, 2 H–C(3)); 1.58 (br. *s*, NH_2). MS: 194 (< 1, $[M - HB]^{+\cdot}$), 121 (9), 120 (100), 103 (12), 101 (71), 91 (11), 82 (14), 80 (15), 77 (7). Anal. calc. for $C_{11}H_{17}BrN_2O$ (273.18): C 48.36, H 6.27, N 10.25; found: C 48.52, H 6.43, N 10.22.

L-*Phenylalanine* N^1,N^1-*(Tetramethylene)amide* (**16**) [31]. To a stirred soln. of Boc-Phe (50 g, 0.188 mol) in CH_2Cl_2 (350 ml) were added under Ar and at 0°, *N*-methylmorpholine (*Fluka*; 22.8 ml, 1.1 equiv.) and isobutyl chloroformate (*Fluka*; 20.1 ml, 1.1 equiv.). The mixture was stirred for 30 min at 0°, followed by addition of pyrrolidine (*Fluka*; 17.1 ml, 1.1 equiv.) and stirring for 30 min at 0° and for 2 h at r.t. Then, the mixture was poured on ice (200 g), 0.5N aq. HCl (300 ml), and AcOEt (500 ml), the org. phase washed with sat. aq. $NaHCO_3$ soln. (2 × 150 ml), brine (400 ml), dried ($MgSO_4$), and evaporated, and the residue dried under reduced pressure over night: 58.8 g (98%) of Boc-Phe-N$(CH_2)_4$ as an amorphous solid, which was added in small portions to a stirred soln. of CF_3COOH (150 ml) under Ar at 0°. The mixture was stirred for 2 h at 0° and evaporated and the residue dried over night and crystallized from Et_2O/hexane 3:1: 53.1 g (85%) of **16**·CF_3COOH. White solid. M.p. 163–164°. $[\alpha]_D = +53.0$ (MeOH, $c = 0.5$). IR (KBr): 3433*w* (br.), 3029*w*, 2978*m*, 2886*m*, 2716*m*, 2610*m*, 1671*s*, 1596*m*, 1506*m*, 1456*m*, 1371*w*, 1207*s*, 1181*s*, 1134*s*, 722*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.25 (br. *s*, 3 NH);

7.4–7.15 (*m*, 5 arom. H); 4.35–4.2 (*m*, H–C(2)); 3.45–3.1 (*m*, 3 aliph. H); 3.1–2.85 (*m*, 2 H–C(3)); 2.6–2.4 (*m*, 1 aliph. H); 1.8–1.4 (*m*, aliph. H). MS: 219 (1, $[M + H]^+$), 127 (46), 120 (100), 99 (14), 91 (14), 70 (24). Anal. calc. for $C_{15}H_{19}F_3N_2O_3$ (332.322): C 54.21, H 5.76, N 8.43; found: C 54.26, H 5.85, N 8.34.

L-*Phenylalanyl*-L-*phenylalanine Dimethylamide* [31] (**17**). To a stirred soln. of Z-Phe (2.28 g, 7.63 mmol) and **15**·HBr (2.29 g, 1.1 equiv.) in CH_2Cl_2 (30 ml) was added under Ar at 0° DCC (1.60 g 7.75 mmol) in small portions and $(i\text{-}Pr)_2EtN$ (1.96 ml, 1.5 equiv.). The mixture was stirred for 30 min at 0° and 6 h at r.t. and poured onto ice and 1N aq. HCl. The org. phase was extracted with sat. aq. $NaHCO_3$ soln. (40 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated and the residue dried under reduced pressure. The crude residue was dissolved in EtOH (50 ml) and AcOH (5 ml) and hydrogenated for 8 h at r.t. using 5% Pd/C (500 mg). The mixture was filtered over *Celite* and evaporated, the residue extracted with CH_2Cl_2 (50 ml) and sat. aq. $NaHCO_3$ soln., the org. fraction dried ($MgSO_4$) and evaporated, and the residue crystallized from Et_2O: 1.75 g (68%) of **17**. M.p. 100.3–101.8°. $[\alpha]_D = -27.5$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3360*m*, 3060*w*, 3025*w*, 2930*m*, 1655*s*, 1640*s*, 1590*m*, 1500*s*, 1452*m*, 1412*m*, 1397*m*, 1340*w*, 1260*w*, 1150*w*, 1108*m*, 915*w*, 875*w*, 745*m*, 705*s*. ^{1}H-NMR ($CDCl_3$, 90 MHz): 7.92 (br. *d*, $J = 7.5$, 1 NH); 7.25 (*s*, 10 arom. H); 5.3–4.95 (*m*, H–C(2.1) or H–C(2.2)); 3.7–3.4 (*m*, H–C(2.2) or H–C(2.1)); 3.2–3.1 (*m*, 2 H–C(3.1) or 2 H–C(3.2)); 2.97 (*d*, $J = 7.5$, 2 H–C(3.2) or 2 H–C(3.1)); 2.83, 2.67 (2*s*, Me_2N); 1.45 (br. *s*, NH_2). MS: 339 (< 1, M^+), 248 (24), 177 (16), 175 (11), 120 (100), 103 (11), 91 (32), 72 (14), 46 (40). Anal. calc. for $C_{20}H_{25}N_3O_2$ (339.44): C 70.77, H 7.42, N 12.38; found: C 70.59, H 7.20, N 12.11.

L-*Phenylalanyl*-L-*phenylalanine* $N^{1,2}$,$N^{1,2}$-*(Tetramethylene)amide* [31] (**18**). To a stirred soln. of Boc-Phe (*Fluka*; 40.0 g, 0.150 mol) in CH_2Cl_2 (400 ml) were added under Ar and ice-bath cooling *N*-methylmorpholine (18.3 ml, 0.166 mol) and isobutyl chloroformate (16.1 ml, 0.166 mol). The mixture was stirred for 30 min at 0°, followed by addition of **16**·CF_3COOH (49.8 h, 0.15 mol) and *N*-methylmorpholine (18.3 ml, 0.166 mol). The mixture was stirred for 30 min at 0° and for 2 h at r.t. and then poured into ice (200 g), 0.5N aq. HCl (300 ml), and AcOEt (500 ml). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (2 × 150 ml) and brine (400 ml), dried ($MgSO_4$), and evaporated, and the residue dried under reduced pressure over night: 64.95 g (93%) of Boc-Phe-Phe-$N(CH_2)_4$. Amorphous solid which was not purified further. This solid was added under Ar in small portions to a stirred soln. of CF_3COOH (150 ml) at 0°. The mixture was stirred for 4 h at 0° and evaporated and the residue dissolved in CH_2Cl_2 (400 ml) and sat. aq. $NaHCO_3$ soln. (300 ml). The aq. phase was extracted with CH_2Cl_2 (2 × 200 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue crystallized from AcOEt/hexane 1:1: 45.0 g (82%) of **18**. White solid. M.p. 102–103°. $[\alpha]_D = -29.8$ ($CHCl_3$, $c = 0.5$). IR (KBr): 3396*w*, 3319*m*, 3060*w*, 3026*w*, 2963*w*, 2930*w*, 2871*w*, 1658*s*, 1634*s*, 1576*w*, 1513*s*, 1452*s*, 1344*w*, 1187*w*, 909*w*, 742*m*, 702*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 6.95 (br. *d*, $J = 7.4$, 1 NH); 7.4–7.1 (*m*, 10 arom. H); 4.91 (*q*, $J = 7.4$, H–C(2.2)); 3.65–3.6 (*m*, H–C(2.1)); 3.5–3.15 (*m*, 3 aliph. H, 1 H–C(3.1)); 2.98 (*d*, $J = 7.4$, 2 H–C(3.2)); 2.7–2.5 (*m*, 1 aliph. H, 1 H–C(3.1)); 1.75–1.5 (*m*, 4 aliph. H); 1.45 (br. *s*, 1 NH_2). MS: 365 (1, M^+), 274 (20), 203 (25), 120 (100), 91 (22), 72 (35). Anal. calc. for $C_{22}H_{27}N_3O_2$ (365.48): C 72.30, H 7.45, N 11.50; found: C 72.03, H 7.45, N 11.52.

X-Ray Structure Analysis. – *Compound* **20f**. $C_{33}H_{37}N_3O_5$. Orthorhombic, $P2_12_12_1$; $a = 10.751$ (8), $b = 14.317$ (9), $c = 18.69$ (2) Å; $D = 1.283$ Mg/m^3, $Z = 4$; $\mu(MoK_\alpha) = 0.081$ mm^{-1}. Data were collected on a *Nicolet-R3m* four-circle diffractometer fitted with a *LT1* cooling apparatus. Temp. 183 K; wavelength 0.71069 Å; scan mode ω; scan speed 1.13°/min minimum speed; strong reflections measured up to 14.65°/min; scan width 0.95°; 2θ range 0–56°; peak to background ratio 5:1; total data measured, 3913 excluding standards; total observed, 3140; rejection criterion $I > 2.5\sigma(I)$; number of parameters; 370 weights $w = 1/\sigma^2(F) + 0.001\,|F|^2$. The structure was determined by direct methods using the SHELXTL PLUS (VAX II) system. The refinement converged at $R = 0.04$ with anisotropic refinement of all non-H-atoms.

Compound **22d**. $C_{41}H_{44}N_4O_5 \cdot H_2O$. Triclinic, $P1$; $a = 6.408$ (5), $b = 11.957$ (6), $c = 13.225$ (7) Å. $\alpha = 65.31$ (4), $\beta = 89.70$ (5), $\gamma = 82.72$ (5)°; $D = 1.26$ Mg/m^3, $Z = 1$; $\mu(MoK_\alpha) = 0.079$ mm^{-1}. Data were collected on a *Nicolet-R3m* four-circle diffractometer fitter with a *LT1* cooling apparatus. Temp. 183 K; wavelength 0.71069 Å; scan mode ω; scan speed 0.9°/min minimum speed; strong reflections measured up to 14.65 °/min; scan width 1.2°; 2θ range 0–56°; peak to background ratio 5:1; total data measured, 4789 excluding standards; total observed, 4257; rejection criterion $I > 2.5\sigma(I)$; number of parameters, 464 weights $w = 1/\sigma^2(F) + 0.001\,|F|^2$. The structure was determined by direct methods using the SHELXTL PLUS (VAX II) system. The refinement converged at $R = 0.047$ with anisotropic refinement of all non-H-atoms.

Compound **21g'**. $C_{40}H_{41}BrN_4O_4 \cdot 0.5\ H_2O$. Orthorhombic, $P2_12_12_1$; $a = 6.408$ (5), $b = 11.957$ (6), $c = 13.225$ (7) Å; $D = 1.22$ Mg/m^3, $Z = 8$; $\mu(CuK_\alpha) = 1.76$ mm^{-1}. Data were collected on a *Nicolet-R3m* four-circle diffractometer fitted with a *LT1* cooling apparatus. Temp. 190 K; wavelength 1.5418 Å; scan mode ω; scan speed 2.9°/min minimum speed; strong reflections measured up to 14.65°/min; scan width 2.6°; 2θ range 0–112°; peak to

background ratio 5:1; total data measured, 5711 excluding standards; total observed, 3117; rejection criterion $I > 2.5\sigma(I)$; number of parameters, 404 weights $w = 1/\sigma^2(F) + 0.001\,|F|^2$. The structure was determined by direct methods using the SHELXTL PLUS (VAX II) system. The refinement converged at $R = 0.078$ with anisotropic refinement of all non-H-atoms. A face-indexed numerical absorption correciton was applied.

The coordinates and geometrical data for these three structures were depositied at the *Cambridge Crystallographic Data Centre,* University Chemical Lab., Cambridge CB2 1EW, UK.

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