104. Transesterifications with 1,8-Diazabicyclo[5.4.0]undec-7-ene/Lithium Bromide (DBU/LiBr) – Also Applicable to Cleavage of Peptides from Resins in *Merrifield* Syntheses

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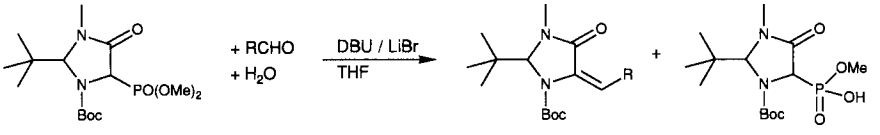
A mixture of the amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and LiBr (preferably 0.5 and 5 equiv., resp.) turns out to be a highly efficient catalyst (at 0–25°) for saponifications (in THF/H_2O) and transesterifications (in ROH). The scope and limitations of the method are determined using *ca.* two dozens of different ester/alcohol combinations (*Schemes 2* and *3*). The investigation is focused on peptides as substrates. Under carefully controlled conditions, no epimerization occurs with *N*-Boc- and *N*-Z-protected peptide esters, when methyl, ethyl, isopropyl, or allyl esters are the products, as shown for peptides containing up to six amino acids, with Ala, Leu, MeLeu, Asp(OEt), or Tyr at the C-terminus (*Scheme 3* and *Tables 1* and *2*). Hydrolytic and transesterifying detachments of Boc-Leu-Ala-Gly-Val-OR and Boc-Leu-Ala-Gly-Phe-OR (R = H, Me) from PAM and *Wang* resins (1–8 h at 0–25°, 2 equiv. of DBU, 5 equiv. of LiBr) can be achieved by this method without epimerization of the C-terminal stereogenic center; a comparison with other methods (HF, $Ti(OR)_4$) is given (*Schemes 4* and *5*). Possible protecting-group strategies involving the DBU/LiBr method are discussed (*Table 3*). Extensive experimental details are given.

In the course of our work on olefinations 'à la *Horner-Emmons-Wadsworth*' [1] with the phosphonate [2] and the highly efficient base system DBU[3])/LiBr [3] shown in *Scheme 1*, we noticed that traces of moisture led to rapid hydrolysis of the phosphonate ester at room temperature. Since such esters are normally not readily hydrolyzed, we embarked on a systematic investigation to test, whether saponifications and transesterifications could be generally effected under these conditions.

There are numerous methods of achieving transesterifications and ester hydrolyses[4]) under acidic and basic conditions, with ester-cleaving enzymes[5]), with titanates[6]), with ion-exchange resins [8], with KF/crown ether [9], and with distannoxane [10] to mention

Scheme 1



[1]) Parts of the Ph.D. theses of *A.T.* (ETH Zürich, Dissertation No. 9454, 1991) and of *D.B.* (ETH Zürich, Dissertation No. 9527, 1991).

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[3]) DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

[4]) See the citations in [4] and [5].

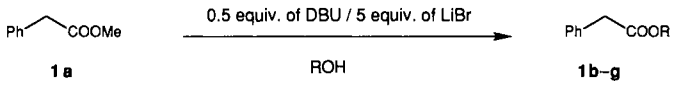
[5]) See ref. 486–489 in [6].

[6]) First described in patents, recently propagated by us [7].

only a few. Also, the amidine base DBU – in solution [11] or polymer-bound [12] – has been recommended as catalyst for transesterifications, with the reactions carried out at elevated temperatures and with long reaction times. Our discovery was indicative of a strong accelerating effect of LiBr, which reminds of the beneficial influence lithium salts may have on the solubility of peptides [13] and on peptide coupling in solution and in solid-phase synthesis [14]. Since DBU/LiBr is known to be a strong base, in fact much stronger than DBU alone (at least in THF [1–3]), special attention was paid to the question, whether such conditions would be applicable to enolizable substrates with stereogenic centers in the α-position to a carbonyl group.

A) Simple Carboxylates. – As representative examples for DBU/LiBr-mediated transesterifications, we chose the esters shown in *Scheme 2*: phenyl acetate **1a**, 4-oxo-

Scheme 2



1a **1b–g**

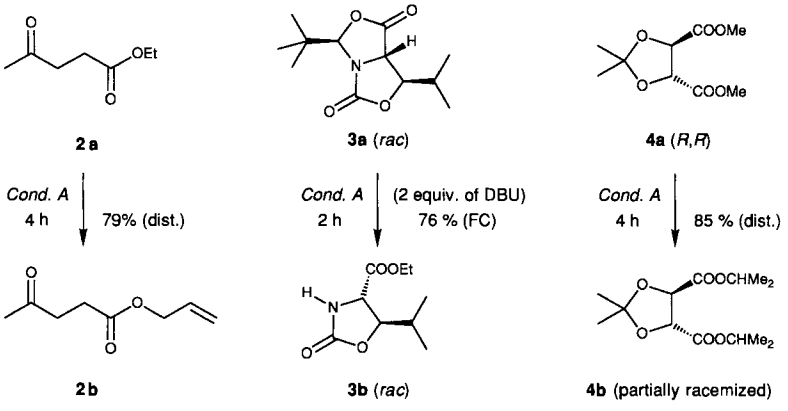
Conditions A: ROH as solvent, room temp.

Conditions B: 1-2 equiv. of ROH in THF/CH_2Cl_2 3:1, 5-Å mol. sieves, reflux temp.

	R	*Conditions*	Reaction time [h]	Yield [%] [a]
1b	Et	*A*	1	90 (dist.)
c [b]	i-Pr	*A*	4	94 (dist.)
d	CH_2=CH–CH_2	*A*	2	98 (GC)
e	(*R*)-Menthyl	*B* (1 equiv.)	24	50 (FC)
f	$MeOCH_2CH_2$	*B* (1 equiv.)	8	93 (GC)
g	$Me_3SiCH_2CH_2$	*B* (2 equiv.)	8	99 (GC)

[a]) Dist., yield of distilled product; GC, yield determined by gas chromatography; FC, yield of product purified by flash chromatography.

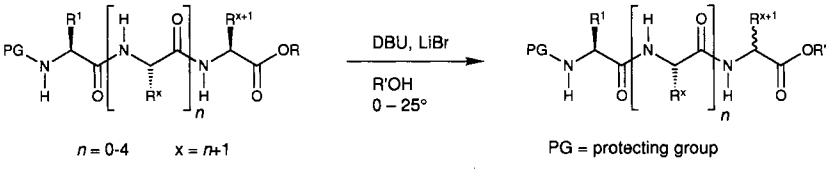
[b]) Reverse reaction (**1c** → **1a**): *Conditions A*, 5 h, 95% (GC).



pentanoate **2a**, a bicyclic urethane **3a** [15], and tartrate acetonide **4a**[7]). With cheap and liquid alcohols, we dissolved the ester to be transesterified in neat alcohol (*ca.* 0.2–0.3M) and observed the reaction rate at room temperature in the presence of 0.5 equiv. of DBU and 2–5 equiv. of LiBr by TLC or GLC analysis of withdrawn samples (→**1b–d**, **2b**, **3b**, **4b**). With valuable alcohols, we used refluxing THF/CH_2Cl_2 as solvent and removed the lower-boiling alcohol formed by trapping in molecular sieves suspended in the vapor phase (see *Exper. Part* and *Scheme 2*). In all cases, transesterification occurred in high yields. With the dioxolanedicarboxylate **4**, extensive racemization took place under these conditions (optical activity of **4b** *ca.* 25%). Methyl 3-oxo-butanoate and methyl bromoacetate could not be transesterified in EtOH or i-PrOH (decomposition): Also, **1a** could not be converted to the *tert*-butyl ester under various conditions (thermodynamically and kinetically unfavorable[8])).

B) Transesterifications of Peptide Esters. – To test the possibility of interconversions between different peptide esters, we used the compounds **5–14** listed in *Scheme 3* as starting materials. They were either prepared 'in house' (**7a**, **8a**, **8b**, **9a**, **10a**, and **11a**) from the corresponding amino acids or by esterification of *N*-protected peptide acids with CH_2N_2 (**5a**, **14a**[9])), or they were supplied to us (**6a**, **12a**[10]), **13a**[11])). The transesterifications were usually carried out by stirring solutions of the peptide esters in the corresponding alcohol in the presence of various amounts of DBU and Li salts at temperatures between 0 and 25°. The conversions were followed by TLC of withdrawn samples, and the degree of epimerization at the C-terminal amino acid of the products (see *Scheme 3*) was deter-

Scheme 3



Starting materials

Boc-Gly-Gly-OMe (**5a**) Z-Gly-Gly-OEt (**6a**) Boc-Phe-Ala-OMe (**7a**)
Boc-Phe-Leu-OMe (**8a**) Boc-Phe-Leu-OCH_2Ph (**8b**) Boc-Phe-Asp(OEt)-OEt (**9a**)
Z-Ala-Leu-OMe (**10a**) Z-Lys(Boc)-Ala-OMe (**11a**) Boc-Ala-Sar-MeLeu-OCH_2Ph (**12a**)
Z-Arg-Lys(Z)-Asp(OCH_2Ph)-Val-Tyr-OCH_2Ph·HCl (**13a**) Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OMe (**14a**)

Products

Boc-Gly-Gly-OEt (**5b**) Boc-Gly-Gly-$OCHMe_2$ (**5c**) Boc-Gly-Gly-OCH_2Ph (**5d**)
Boc-Phe-Ala-OEt (**7b**) Boc-Phe-Ala-$OCHMe_2$ (**7c**) Boc-Phe-Ala-$OCH_2CH{=}CH_2$ (**7d**)
Boc-Phe-Ala-$OCMe_3$ (**7e**) Boc-Phe-Leu-OEt (**8c**) Boc-Phe-Leu-$OCHMe_2$ (**8d**)
Boc-Phe-Asp(OMe)-OMe (**9b**) Z-Ala-Leu-OEt (**10b**) Z-Ala-Leu-$OCHMe_2$ (**10c**)
Z-Lys (Boc)-Ala-$OCH_2CH{=}CH_2$ (**11b**) Boc-Ala-Sar-MeLeu-OMe (**12b**)
Z-Arg-Lys(Z)-Asp(OMe)-Val-Tyr-OMe·HCl (**13b**) Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OEt (**14b**)

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[7]) Compare with the non-racemizing titanate transesterification **4a**→**4b** [16] in i-PrOH heated at reflux.

[8]) *Cf.* the unsuccessful attempts to prepare *tert*-butyl esters under titanate catalysis [7].

[9]) The peptide acids Boc-Gly-Gly-OH and Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OH and the ester **6a** were generously supplied to us by *Sandoz Pharma AG*, Basel (Dr. *R. Wenger*).

[10]) Prepared by *H. Gründler* [17].

[11]) Supplied by *Cilag AG*, Schaffhausen (Dr. *H. Lehner*).

mined by their total hydrolysis to free amino acids and GC analysis of the *N*-pentafluoropropionyl isopropyl esters on the chiral stationary phase *Chirasil-Val®* [18].

As can be seen from *Table 1*, long reaction times and/or high temperatures lead to extensive epimerizations, not only of the C-terminal amino acid in Boc-Phe-Ala-OR but also of the N-terminal one (first two entries). On the other hand, use of the mildest possible conditions leads to rapid transesterification with practically no epimerization when going from methyl to ethyl, isopropyl, or allyl esters. In most cases, LiBr was used as the salt additive with the substrate **7a**, but LiCl and $LiClO_4$ work equally well[12]). Again, *tert*-butyl esters cannot be prepared, see last entry of *Table 1*. $LiBF_4$, the Li-salt with the least nucleophilic anion, does not act as an accelerator in this DBU-catalyzed reaction[13]).

Table 1. *Transesterification of Boc-Phe-Ala-OMe* (**7a**) *to Boc-Phe-Ala-OR in ROH with DBU/LiX, Using Different Reaction Conditions*

Conditions					Product			
Alcohol	Salt [equiv.]	DBU [equiv.]	Temp. [°]	Time	No.	Yield [%]	Starting mat. [%][a])	Ratio L-Ala/D-Ala[b])
MeOH	10 LiBr	2	25	4 d	**7a**[c])	81	–	54:46[d])
MeOH	10 LiBr	2	65	3 h	**7a**[c])	68[e])	–	52:48[f])
EtOH	5 LiBr	0.5	25	6 min	**7b**	96	⩽2	96:4
EtOH	5 LiBr	0.5	25	90 min	**7b**	97	⩽2	84:16
Me_2CHOH	5 LiBr	0.5	25	90 min	**7c**	93	⩽2	83:17
Me_2CHOH	5 $LiClO_4$	0.5	25	90 min	**7c**	94	⩽2	74:26
Me_2CHOH	5 $LiBF_4$	0.5	25	90 min	**7c**	7[g])	93	–
Me_2CHOH	5 LiBr	0.5	25	45 min	**7c**	95	9	92:8
Me_2CHOH	2 LiBr	0.5	25	90 min	**7c**	95	⩽2	87:13
Me_2CHOH	2 LiBr	2	25	90 min	**7c**	92	⩽2	82:18
Me_2CHOH	5 LiBr	0.5	–10	44 h	**7c**	88	4	96:4
Me_2CHOH	5 LiBr	0.5	0	16 h	**7c**	88	⩽2	95:5
$CH_2=CHCH_2OH$	5 LiBr	0.5	0	6 h	**7d**	91	3	95:5
Me_3COH	5 LiBr	0.5	25	54 h[h])	**7e**	12[g])	88	55:45[i])

[a]) The amount of starting material was determined by ^{1}H-NMR spectroscopy.
[b]) The degree of epimerization in the peptide follows from the determination of enantiomeric purity of the free amino acids (see text and *Exper. Part*).
[c]) The ratio of L- to D-alanine of the starting material **7a** was 97:3.
[d]) The L- to D-phenylalanine ratio was 90:10.
[e]) After flash chromatography (no enrichment of a diastereoisomer).
[f]) The L- to D-phenylalanine ratio was 72:28.
[g]) Judged from the ^{1}H-NMR spectrum.
[h]) A 1:1 mixture of Me_3COH and THF was used as solvent.
[i]) Ratio of the two diastereoisomers (L,L and L,D) by ^{1}H-NMR.

Neither DBU in the absence of LiBr, nor Et_3N or $(i\text{-}Pr)_2NEt$ (*Hünig* base) in the presence of LiBr, nor LiBr alone cause transesterifications to any appreciable extent under the conditions used for the DBU/LiBr-mediated reaction.

Having tested the best conditions for epimerization-free transesterifications with the dipeptide ester **7a**, we applied them to the other peptide derivatives (see *Table 2*).

[12]) $ZnCl_2$/DBU (5 and 0.5 equiv., 90 min, 25°) does not effect the reaction **7a**→**7c**.
[13]) $Ca(OAc)_2$ has been reported to effect transesterifications of peptide esters in MeOH at room temperature [19].

Table 2. *Transesterification of the Peptides* **5a**, **6a**, *and* **8a–14a** *in ROH Using 5 Equiv. of LiBr and 0.5 Equiv. of DBU*

Conditions				Product			
Starting mat.[a])	Alcohol	Temp. [°]	Time	No.	Yield [%]	Starting mat. [%][b])	Ratio of L/D C-terminal amino acid[c])
5a	EtOH	25	4 h	**5b**	67	⩽ 2	–
5a	Me_2CHOH	25	72 h	**5c**	75[d])	⩽ 2	–
5a	$PhCH_2OH$	25	72 h	**5d**	42[d])	7	–
6a	EtOH	25	66 h	**6a**	60	–	–
8a (98:2)	EtOH	25	6 min	**8c**	97	7	97:3
8a (98:2)	Me_2CHOH	25	90 min	**8d**	93	4	87:13
8a (98:2)	$PhCH_2OH$	3	7 d	**8b**	88[e])	6[f])	73:27[f])
8b (96:4)	MeOH	25	20 h	**8a**	90	⩽ 2	69:31
8b (96:4)	MeOH	3	21 h	**8a**	61[g])	⩽ 2	94:6
9a (89:11)	MeOH	0	30 min	**9b**	94	4	85:15
10a (98:2)	MeOH	25	20 h	**10a**	73	–	–
10a (98:2)	EtOH	25	6 min	**10b**	93	10	97:3
10a (98:2)	Me_2CHOH	25	90 min	**10c**	85	5	91:9
11a (98:2)	$CH_2=CHCH_2OH$	0	22 h	**11b**	93	3	85:15
12a	MeOH	3	50 h	**12b**	91	⩽ 2	–
13a (97:3)	MeOH[h])	3	24 h	**13b**	89	⩽ 5[e])	97:3[e])
14a (98:2)	EtOH	0	1 h	**14b**	95[d])	⩽ 5[i])	97:3[i])

[a]) L/D Ratio of C-terminal amino acid of the starting material in parentheses.
[b]) The amount of starting material was determined by ^{1}H-NMR spectroscopy.
[c]) The degree of epimerization in the peptide follows from the determination of enantiomeric purity of the free amino acids (see text and *Exper. Part*).
[d]) After flash chromatography.
[e]) After recrystallization.
[f]) Prior to recrystallization.
[g]) Determined by ^{1}H-NMR (39% of $PhCH_2OH$).
[h]) Additional 5 equiv. of LiBr and twofold dilution with THF were necessary in order to solubilize **13a**.
[i]) Prior to flash chromatography.

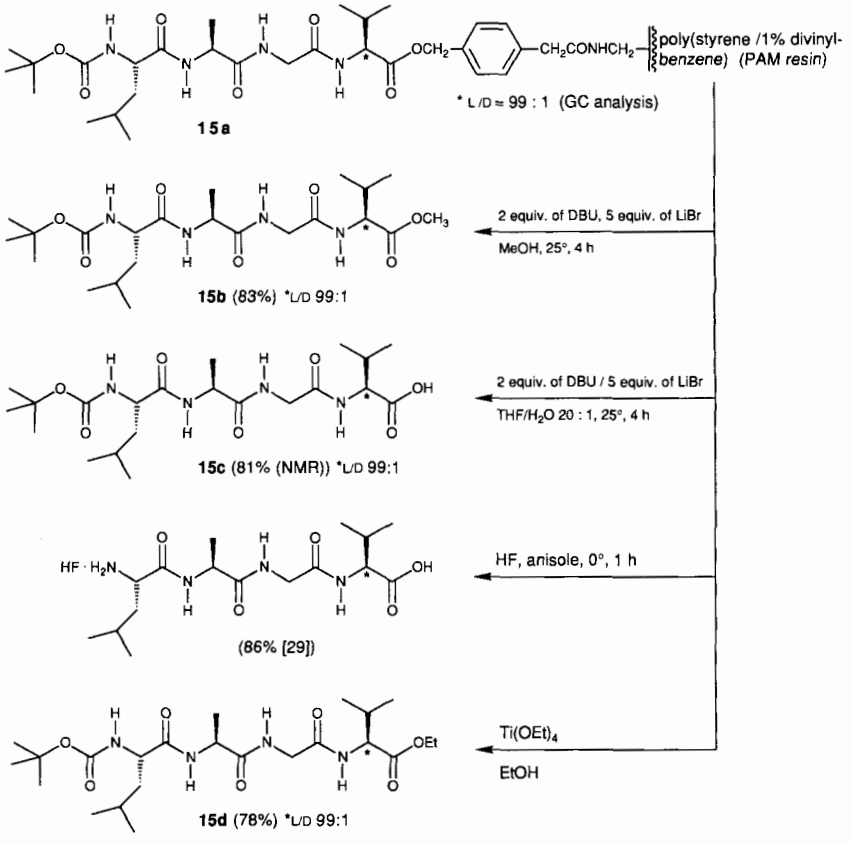
Inspection of the data in *Table 2* leads to the following conclusions: *i*) both Boc- and Z-protecting groups may be at the N-terminus, with the latter being somewhat less stable under our transesterification conditions; *ii*) ester groups in the side-chain of aspartate units also undergo RO exchange (**9a**→**9b**); *iii*) the method is especially well applicable when going from methyl to ethyl or *vice versa* and from benzyl to methyl ester; *iv*) benzyl esters of peptides cannot be prepared in this way without appreciable epimerization; *v*) allyl ester may (*Table 1*) or may not (*Table 2*) be formed without epimerization.

C) Detachment of Peptides from PAM and *Wang* Resins by DBU/LiBr-Mediated Saponification and Transesterification. – There are numerous publications describing peptide-(polystyrene resin) cleavage leading directly to peptide esters, *e.g.* with NH_3/MeOH [20], with Et_3N/ROH [21], with ion-exchange resins [22], with 2-(dimethylamino)ethanol/TlOEt [23], with KCN/ROH [24], or with titanates [25]. In all these cases, reactions are carried out using either elevated temperatures or long reaction times, and they often provide relatively low yields. In the most commonly used procedures for the peptide-(polystyrene resin) cleavage leading to the peptide acid, strong acids such as HF are utilized. As industrial applications of *Merrifield* solid-phase peptide syntheses

emerge, methods avoiding the hazardous HF become more and more important. Reports on the use of basic conditions for 'resin cleavage' of free peptide acids involve, *e.g.* 0.5M NaOH/dioxane/H_2O_2 [26] or $Bu_4NF \cdot H_2O$/DMF[14]) [27][15]).

To test the possibility of peptide cleavage from a resin using the transesterification method described here, *i.e.* DBU/LiBr in alcohol, we employed Boc-Leu-Ala-Gly-Val-(PAM resin[16])) (**15a**) and Boc-Leu-Ala-Gly-Phe-(PAM resin) (**16a**) as starting materials, where the peptide is bonded to the resin *via* a benzyl-ester linkage. The peptide-resin cleavage reactions were carried out by stirring suspensions of the peptide resins in MeOH or THF/H_2O in the presence of 2 equiv. of DBU and 5 equiv. of LiBr at temperatures between 0 and 25°. The degree of epimerization at the C-terminal amino acid was determined as discussed in *Sect. B.* As can be seen from *Scheme 4*, the methyl ester **15b** was set free within 4 h from the peptide resin **15a** in 83% yield without any epimerization.

Scheme 4

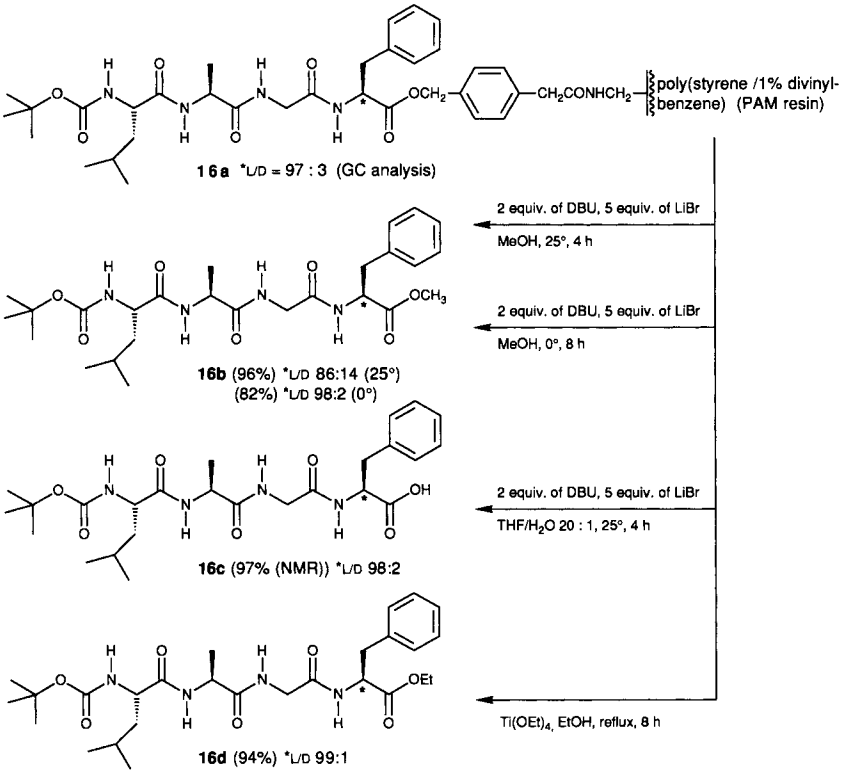


[14]) Cleavage method for the PAM resin[16]), the peptide–resin bond of which is one of the most acid-stable ones.
[15]) For reviews of conventional peptide-resin cleavage methods, see [28].
[16]) PAM resin = {[4-(hydroxymethyl)phenyl]acetamido}methyl-substituted poly(styrene/1% divinylbenzene).

Utilizing THF/H_2O instead of MeOH led to the peptide acid **15c** in 81% yield (^1H-NMR) in the same time required for the preparation of **15b**, again without epimerization. These conversions can be compared either to the cleavage with HF [29] leading to the fully deprotected peptide in 86% yield within 1 h at 0°, or to the reaction of **15a** with $Ti(OEt)_4$ leading to the Boc-protected ethyl ester **15d** without epimerization in 78% yield after 7 h of reflux in EtOH (reaction times are generally not optimized).

Cleavage of the more epimerization-prone Phe-containing peptide-resin **16a** to the peptide esters **16b** and **16d** and to the peptide acid **16c** generally proceeded in better yields than in the case of the Val-bonded **15a** under the same conditions (*Scheme 5*), due to less

Scheme 5



steric hindrance. The cleavage of **16a** in MeOH at room temperature led to a considerable level of epimerization of the Phe moiety of **16b** (14%); however, carrying out the reaction at 0° led to **16b** without any detectable epimerization. As expected, peptide-resin cleavage to the peptide acid **16c** occurred without any epimerization, due to the greater configurational stability of the resulting peptide salt (RCO_2^- $DBUH^+$).

In preliminary experiments, the conversion of Fmoc-Leu-Ala-Gly-Val-(*Wang* resin) to the fully deprotected peptide with DBU/LiBr in THF/H_2O led to yields comparable to those of the conventional cleavage (piperidine/*N*,*N*-dimethylformamide and then

CF_3COOH) as shown by integration of the HPLC peaks of the crude reaction mixtures after filtration[17]).

It is to be expected that by using DBU/LiBr in different solvents, with different anchoring and protecting groups, either free, partially, or fully protected peptides may be obtained directly from the fully protected peptide resin (*Table 3*). This may prove to be very useful in the growing area of peptide segment coupling, when partially or fully protected segments are condensed.

Table 3. *Possible Protecting-Group Strategies Leading to Either Deprotected, Partially, or Fully Protected Peptides Using DBU/LiBr for Peptide-Resin Cleavage*

Product	Solvent	Type of resin	Side-chain protection	Amino acid (AA) used	Last introduced AA
Fully protected	ROH	*Wang*	base stable[a])	Fmoc-AA	Boc-AA
Fully deprotected	H_2O/THF	PAM	base labile	Boc-AA	Fmoc-AA
N-protected	H_2O/THF	PAM	base labile	Boc-AA	Boc-AA
C-protected	ROH	PAM	base labile	Boc-AA	Fmoc-AA
N,C-protected	ROH	PAM	base labile	Boc-AA	Boc-AA
Side-chain- and N-protected	H_2O/THF	*Wang*	base stable	Fmoc-AA	Boc-AA
Side-chain- and C-protected	ROH	*Wang*	base stable	Fmoc-AA	Fmoc-AA
Side-chain-protected	H_2O/THF	*Wang*	base stable	Fmoc-AA	Fmoc-AA

[a]) *E.g.* Boc and *t*-Butyl protecting groups.

We thank Mr. *Ch. Beerli* (Preclinical Research, *Sandoz Pharma AG*, Basel) for the preparation of peptide resins and the *Sandoz AG* for financial support.

Experimental Part

1. *General.* Inorganic salts were dried at 180° under high vacuum (h.v.) and stored in a desiccator over P_2O_5. THF was freshly distilled from K under Ar. Other solvents were purchased from *Fluka AG* (*puriss.*). DBU was distilled from CaH_2 and stored under Ar. Flash chromatography (FC): *Merck* silica gel *60* (40–63 mm). GC (amino acids): *Chirasil-Val®* column (*Macherey-Nagel*, 25 m, 0.4 mm), *Carlo-Erba-Fractovap-4160-HR* GC; injector temp. 160°, detector temp. 180° (FID); carrier gas, 0.5 bar H_2; temp. program: 3 min at 85°, 4°/min till 180°. GC (simple carboxylates): *Pluronic L-64* (19 m, 0.17 mm) cap. column, *Carlo-Erba-Fractovap-4160-HR* GC; injector temp. 200°, detector temp. 200° (FID), carrier gas: N_2; temp. program: 1 min at 70°, 20–30°/min, 4 min at 160°; the relative peak intensities are given either as peak areas (*I*) or as the contributions (%) of the peaks in question with respect to all peaks of the chromatogram. M.p.: *Büchi-510* apparatus; uncorrected. IR spectra: *Perkin-Elmer-241* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker-WM-300* (300 and 75 MHz, resp.), *Varian-Gem-200* (200 MHz), *Varian-EM-390* (90 MHz); $CDCl_3$ solns., δ in ppm rel. to internal Me_4Si, *J* in Hz and integrals (*I*) relative to each other. FAB-MS: *VG-ZAB2-SEQ* in a 3-nitrobenzyl-alcohol matrix; in *m/z* (% of basis peak). Peptide numbering according to [30].

2. *General Procedure for Transesterification of Simple Carboxylates.* 2.1. *Conditions A*: LiBr (5 equiv.) and the starting carboxylate ester (1 equiv.) were dissolved under dry Ar in the appropriate quantity of the desired absolute alcohol, so that a 0.2–0.3M concentration of substrate was obtained. Freshly distilled DBU (0.5 equiv.) was then added to this soln., and stirring was continued at r.t., the course of the reaction being monitored by TLC or GC. When transesterification attained completion, the mixture was evaporated and hydrolyzed with a sat. aq. NH_4Cl soln. or 1N HCl. The product was extracted with 2 portions of Et_2O, the combined org. fractions washed with brine to neutrality, dried (Na_2SO_4), and evaporated, and the crude product purified by distillation or FC.

[17]) Results not described in the *Exper. Part.*

2.2. *Conditions B*: With valuable alcohols, LiBr (5 equiv.), the methyl ester (1 equiv.), and a stoichiometric amount of the alcohol (1 to 2 equiv.) were dissolved in THF/CH_2Cl_2 3:1 according to *Conditions A*. The mixture was then refluxed under dry Ar, the MeOH liberated by the reaction being trapped in 5-Å molecular sieves filled in a dropping funnel placed between the reaction flask and the refluxing condenser. The course of the reaction was monitored by TLC or GC, and when transesterification reached completion, the mixture was worked up as described above.

3. *General Procedure for Workup of Peptide Esters*. The reaction mixture was added to 200 ml of AcOEt (150 ml of AcOEt in a second separatory funnel), the extract washed successively with 1N HCl (100 ml), 1N HCl (50 ml), 1M $KHCO_3$ (100 ml), 1M $KHCO_3$ (50 ml), and H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated, and the residue dried for several h under reduced pressure.

4. *General Procedure for the Preparation of Amino-Acid Derivatives for GC Analyses*. In a screw-capped vial, 10 mg of peptide were hydrolyzed with conc. HCl soln. at 110° for 8 h. Then, H_2O was removed in an airflow, 1 ml of a soln. of AcCl (5.7 ml) and Me_2CHOH (10 ml, prepared at 0°) were added, and the vial was tightly closed. Heating at 110° for 1 h, removing of excess reagent in an airflow and further reaction with $(CF_3CF_2CO)_2O$ (80 µl) in CH_2Cl_2 (200 µl) for 20 min gave, after removing of excess reagent in an airflow, the derivatives of the individual amino acids. This crude mixture was dissolved in Et_2O and injected directly into the *Chirasil-Val®* column.

5. *Transesterifications of Simple Carboxylates. Ethyl Phenylacetate* (**1b**). According to *2.1*, with **1a** (4.51 g, 30 mmol), LiBr (13.03 g, 150 mmol), EtOH (150 ml), and DBU (2.28 g, 15 mmol) at r.t. for 1 h. Distillation *in vacuo* afforded 4.40 g (90%) of pure **1b**. B.p. 65.5–66°/1 Torr. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.13 (*t*, *J* = 6.6, CH_3CH_2O); 3.62 (*s*, CH_2); 4.15 (*q*, *J* = 6.6, CH_3CH_2O); 7.30 (*s*, Ph).

Isopropyl Phenylacetate (**1c**). As described above for **1b**, **1a** (4.51 g, 30 mmol) was transesterified in Me_2CHOH for 4 h at r.t. Distillation *in vacuo* afforded 5.04 g (94%) of **1c**, ⩾ 96% pure (^{1}H-NMR). B.p. 75–77°/0.5 Torr. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.27 (*d*, *J* = 6.0, $(CH_3)_2CHO$); 3.60 (*s*, CH_2); 5.02 (*sept.*, *J* = 6.0, $(CH_3)_2CHO$); 7.32 (*s*, Ph).

Allyl Phenylacetate (**1d**). According to *2.1*, with **1a** (300 mg, 2 mmol), LiBr (869 mg, 10 mmol), allyl alcohol (10 ml), and DBU (150 µl, 1 mmol) at r.t. Samples of 1 ml of the mixture were withdrawn after 30, 60, 90, 120, and 180 min, hydrolyzed, worked up, and analyzed by GC. Transesterification was essentially complete after 2 h (98% of **1d** according to GC). ^{1}H-NMR (90 MHz, $CDCl_3$): 3.63 (*s*, CH_2); 4.56 (*d*, *J* = 6.0, CH_2=CHCH_2); 5.10–5.40 (*m*, CH_2=CHCH_2); 5.63–6.15 (*m*, CH_2=CHCH_2); 7.27 (*s*, Ph).

(R)-*Menthyl Phenylacetate* (**1e**). According to *2.2*, with **1a** (751 mg, 5 mmol), LiBr (2.17 g, 25 mmol), (–)-(*R*)-menthol (781 mg, 5 mmol), THF/CH_2Cl_2 3:1 (20 ml), and DBU (0.37 ml, 2.5 mmol) at reflux temp. According to TLC (SiO_2, pentane/Et_2O 4:1), transesterification was not complete after 24 h. Nervertheless, the mixture was hydrolyzed and worked up. FC (SiO_2, pentane/Et_2O 4:1) afforded 691 mg (50%) of **1e** as an oil which was essentially pure (^{1}H-NMR). R_f (SiO_2, pentane/Et_2O 4:1) 0.84. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.60–2.16 (*d*, *t* and *m*, 18 H, CH, CH_2, CH_3 of menthyl); 3.57 (*s*, PhCH_2); 4.67 (*m*, CHO of menthyl); 7.27 (*s*, Ph).

2-Methoxyethyl Phenylacetate (**1f**). As described above for **1e**, with **1a** (751 mg, 5 mmol), 2-methoxyethanol (380 mg, 0.4 ml, 5 mmol), THF/CH_2Cl_2 3:1 (20 ml), and LiBr/DBU for 8 h under reflux. The crude **1f** was *ca.* 93% pure (GC) and still contained *ca.* 7% of **1a** (GC, ^{1}H-NMR). ^{1}H-NMR (90 MHz, $CDCl_3$): 3.35 (*s*, MeO); 3.57 (*t*, *J* = 5, $CH_3OCH_2CH_2$); 3.65 (*s*, PhCH_2); 4.23 (*t*, *J* = 5, $MeOCH_2CH_2O$); 7.30 (*s*, Ph).

2-(Trimethylsilyl)ethyl Phenylacetate (**1g**). As described above for **1e**, with **1a** (751 mg, 5 mmol), 2-(trimethylsilyl)ethanol (1.18 g, 1.43 ml, 10 mmol), THF/CH_2Cl_2 3:1 (20 ml) and LiBr/DBU under reflux for 8 h. Crude **1g** obtained in quantitative yield was essentially pure (⩾ 99% pure by GC). ^{1}H-NMR (90 MHz, $CDCl_3$): 0.10 (*s*, Me_3Si); 1.03 (*t*, *J* = 8.2, $Me_3SiCH_2CH_2$); 3.63 (*s*, PhCH_2); 4.23 (*t*, *J* = 8.2, $Me_3SiCH_2CH_2$); 7.33 (*s*, Ph).

Allyl 4-Oxopentanoate (**2b**). According to *2.1*, with **2a** (4.33 g, 30 mmol) and allyl alcohol (120 ml) at r.t. for 4 h. Distilation *in vacuo* yielded 3.73 g (79%) of **2b**, ⩾ 96% pure (^{1}H-NMR). B.p. 92°/11 Torr. ^{1}H-NMR (90 MHz, $CDCl_3$): 2.20 (*s*, MeO); 2.70 (*m*, CH_2CH_2); 4.57 (*d*, *J* = 6.0, CH_2=CHCH_2); 5.13–5.46 (*m*, CH_2=CHCH_2); 5.66–6.17 (*m*, CH_2=CHCH_2).

*Methyl (4*RS,*5*SR*)-5-Isopropyl-2-oxooxazolidine-4-carboxylate* (**3b**). According to *2.1*, with *rac*-**3a** (302 mg, 1.25 mmol), LiBr (543 mg, 6.25 mmol), EtOH (30 ml), and DBU (0.37 ml, 2.5 mmol; 2 equiv.) at r.t. for 2 h. FC (SiO_2, CH_2Cl_2/AcOEt 4:1) afforded 192 mg (76%) of *rac*-**3b**. Colorless viscous oil. IR (KBr): 3460*m*, 3300–3100*w* (br.), 2980*s*, 2940*w*, 1765*s*, 1750*s* (br.), 1470*w*, 1450*w*, 1380*m*, 1220*m* (br.), 1130*m*, 1045*m*. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.03 (*d*, *J* = 7.5, $(CH_3)_2CH$); 1.30 (*t*, CH_3CH_2O); 1.97 (*m*, $(CH_3)_2CH$); 4.03 (*d*, *J* = 4.5, H–C(4)); 4.16 (*q*, CH_3CH_2O); 4.37 (*dd*, H–C(5)); 6.26 (*s*, NH).

*Diisopropyl (2*R,*3*R*)-2,3-O-Isopropylidenetartrate* (**4b**). According to *2.1*, with **4a** (4.37 g, 20 mmol) and Me_2CHOH (70 ml) at r.t. for 4 h. Distillation *in vacuo* afforded 4.69 g (85%) of extensively racemized **4b**. B.p.

110–112°/0.2 Torr ([16]: 80°/0.001 Torr). $[\alpha]_D = -11.8$ ($c = 4.25$, $CHCl_3$) ([16]: $[\alpha]_D = +40.8$ ($c = 3.80$, $CHCl_3$) for the (2*S*,3*S*)-enantiomer).

6. *Preparation of the Peptide Starting Materials. Boc-Gly-Gly-OMe* (**5a**). A suspension of Boc-Gly-Gly-OH (5.81 g, 26 mmol) and $NaHCO_3$ (4.2 g, 50 mmol) in DMF (125 ml) was treated with a soln. of MeI (7.78 ml, 125 mmol) in DMF (125 ml) at r.t. After stirring for 31 h, H_2O was added and the mixture extracted with AcOEt, washed with H_2O, dried (Na_2SO_4), and evaporated. The crude product was purified by FC (AcOEt/hexane 9:1): 3.90 g (63%) of **5a** as an oil after drying overnight. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.45 (*s*, *t*-Bu); 3.72 (*s*, MeO); 3.81, 4.05 (2*d*, $J = 6$, CH_2(2.1), CH_2(2.2)); 5.10–5.38, 6.51–6.80 (2*m*, NH(2.1), NH(2.2)). ^{13}C-NMR ($CDCl_3$): 28.31 ($(CH_3)_3C$); 41.10, 44.22 (CH_2(2.1), CH_2(2.2)); 52.41 (MeO); 80.41 ($(CH_3)_3C$); 156.11 (OCON); 169.91, 170.21 (C(1.1), C(1.2)).

Boc-Phe-Ala-OMe (**7a**). A soln. of Boc-Phe-OH (10.61 g, 40 mmol) and *N*-methylmorpholine (NMM; 4.4 ml, 40 mmol) in THF (90 ml) was cooled to –15° and treated under stirring with ethyl chloroformate (3.8 ml, 40 mmol). After 8 min, a cooled soln. of HCl · H-Ala-OMe (6.14 g, 44 mol) in THF (180 ml), neutralized 5 min prior to addition with NMM (4.84 ml, 44 mmol) and dissolved with H_2O (5 ml), was added. After 2 h of stirring and allowing to reach r.t., the mixture was worked up according to *Exper. 3* (double amount of solvent), and the crude product was recrystallized from hexane (and a little AcOEt) leading to 12.9 g (92%) of **7a** with a m.p. of 109–110° and a D-Ala-portion of 3% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.33 (*d*, $J = 7.2$, CH_3(3.2)); 1.38 (*s*, *t*-Bu); 3.05 (*d*, $J = 6.6$, CH_2(3.1)); 3.69 (*s*, MeO); 4.30–4.45 (*m*, H–C(2.1)); 4.51 (*dq*, $J = 7.2$, 7.2, H–C(2.2)); 5.10 (*d*, $J = 8.0$, NH(2.1)); 6.38 (*d*, $J = 7.0$, NH(2.2)); 7.14–7.32 (*m*, Ph). ^{13}C-NMR ($CDCl_3$): 18.35 (CH_3(3.2)); 28.27 ($(CH_3)_3C$); 38.40 (CH_2(3.1)); 48.13, 55.62 (H–C(2.1), H–C(2.2)); 52.44 (MeO); 80.25 ($(CH_3)_3C$); 126.96, 128.64, 129.42, 136.58 (Ph); 155.40 (OCON); 170.82, 172.89 (C(1.1), C(1.2)). MS (among others): 701 (9), 352 (17), 351 (65), 296 (17), 295 (82), 252 (17), 251 (90), 164 (21), 154 (11), 137 (9), 136 (9), 136 (12), 121 (13), 120 (100), 104 (38), 102 (10), 91 (14), 77 (9), 57 (65). GC: 210 (D-Ala, 0.144%), 226 (L-Ala, 4.461%).

Boc-Phe-Leu-OMe (**8a**). As described for **7a**, with Boc-Phe-OH (6.63 g, 25 mmol), NMM (2.75 ml, 25 mmol), THF (60 ml), ethyl chloroformate (2.4 ml, 25 mmol), and HCl · H-Leu-OMe (4.99 g, 27.5 mmol) in THF (120 ml; neutralized with NMM (3.02 ml, 27.5 mmol) and dissolved with H_2O) for 24 h. Recrystallization from hexane led to 9.81 g (93%) of **8a** with a m.p. of 98–104° and a D-Leu portion of 2% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.89 (*d*, $J = 6$, CH_3(5.2)); 0.91 (*d*, $J = 6$, CH_3(5.2)); 1.41 (s, *t*-Bu); 1.42–1.65 (*m*, H–C(4.2), CH_2(3.2)); 3.07 (*d*, $J = 7$, CH_2(3.1)); 3.69 (MeO); 4.34 (*td*, $J = 7$, 7, H–C(2.1 or 2.2)); 4.50–4.63 (*m*, H–C(2.1 or 2.2)); 4.92–5.08 (*m*, NH(2.1); 6.25 (*d*, $J = 8$, NH(2.2)); 7.17–7.35 (*m*, Ph). ^{13}C-NMR ($CDCl_3$): 21.88, 22.73 (2 CH_3(5.2)); 24.64 (H–C(4.2)); 28.23 ($(CH_3)_3C$); 38.07 (CH_2(3.1)); 41.60 (CH_2(3.2)); 50.73, 55.71 (H–C(2.1), H–C(2.2)); 52.21 (MeO); 80.28 ($(CH_3)_3C$); 126.93, 128.64, 129.39, 136.59 (Ph); 155.5 (OCON); 170.92, 172.83 (C(1.1), C(1.2)). MS (among others): 393 (17), 338 (9), 337 (40), 294 (15), 293 (74), 164 (15), 146 (40), 144 (8), 133 (12), 131 (11), 121 (11), 120 (100), 91 (14), 86 (79), 57 (67). GC: 473 (D-Leu, 0.752%), 521 (L-Leu, 36.411%).

Boc-Phe-Leu-OCH$_2$Ph (**8b**). As described for **7a**, with Boc-Phe-OH (5 g, 19 mmol), NMM (2.1 ml, 19 mmol), THF (40 ml), ethyl chloroformate (1.79 ml, 18.9 mmol), and soln. of TsOH · H-Leu-OCH$_2$Ph (7.79 g, 19.8 mmol) in THF (100 ml, neutralized with NMM (2.2 ml, 20 mmol) and dissolved with H_2O (5 ml)) for 21 h. Recrystallization from hexane led to 8.1 g (91%) of **8b** with a m.p. of 81–82° and a D-Leu portion of 4%. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.87 (*d*, $J = 6$, CH_3(5.2)); 0.89 (*d*, $J = 6$, CH_3(5.2)); 1.41 (*s*, *t*-Bu); 1.40–1.73 (*m*, H–C(4.2), CH_2(3.2)); 3.05 (*d*, $J = 7$, CH_2(3.1)); 4.35 (*td*, $J = 7$, 7, H–C(2.1 or 2.2)); 4.55–4.68 (*m*, H–C(2.1 or 2.2)); 4.93–5.08 (*m*, NH(2.1)); 5.12 (*s*, PhCH_2); 6.29 (*d*, $J = 8$, NH(2.2)); 7.15–7.43 (*m*, 2 Ph). ^{13}C-NMR ($CDCl_3$): 21.88, 22.73 (2 CH_3(5.2)); 24.67 (CH(4.2)); 28.23 ($(CH_3)_3C$); 38.11 (CH_2(3.1)); 41.53 (CH_2(3.2)); 50.89, 55.68 (H–C(2.1), H–C(2.2)); 67.01 (PhCH_2O); 126.91, 128.22, 128.42, 128.61, 129.39, 135.38, 136.60 (*Ph*–C(3.1), *Ph*CH_2O); 155.3 (OCON); 170.98, 172.25 (C(1.1), C(1.2)). MS (among others): 469 (10), 413 (21), 370 (10), 369 (37), 222 (9), 210 (14), 164 (11), 120 (40), 92 (12), 91 (100), 86 (50), 57 (43). GC: 476 (D-Leu, 1.209%), 530 (L-Leu, 32.671%).

Boc-Phe-Asp(OEt)-OEt (**9a**). As described for **7a**, with Boc-Phe-OH (1.326 g, 5 mmol), NMM (0.55 ml, 5 mmol), THF (15 ml), ethyl chloroformate (0.57 ml, 6 mmol), and HCl · H-Asp(OEt)-OEt (1.184 g, 5.25 mmol) in THF (20 ml; neutralized with NMM (0.58 ml, 5.25 mmol) and dissolved with H_2O (0.5 ml)) for 19.5 h. FC (AcOEt/hexane 1:1.5) and recrystallization from hexane led to 1.045 g (48%) of **9a** with a m.p. of 91–94° and a D-Asp portion of 11% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.24, 1.25 (2*t*, $J = 7.2$, 2 CH_3CH$_2$); 1.40 (*s*, *t*-Bu); 2.79, 2.99 (2*dd*, $J = 4$, 17, 2 H–C(3.2)); 3.09 (*d*, $J = 6$, CH_2(3.1)); 4.11, 4.19 (2*q*, $J = 7.2$, CH_3CH_2); 4.30–4.48 (*m*, H–C(2.1 or 2.2)); 4.76 (*dt*, $J = 5$, 8, H–C(2.1 or 2.2)); 4.88–5.00 (*m*, NH(2.1)); 6.85 (*d*, $J = 7.5$, NH(2.2)); 7.17–7.30 (*m*, Ph). ^{13}C-NMR ($CDCl_3$): 14.06, 14.09 (2 CH_3CH_2); 28.24 ($(CH_3)_3C$); 36.29, 38.30 (CH_2(3.1), CH_2(3.2)); 48.72, 55.48 (H–C(2.1), H–C(2.2)); 60.99, 61.85 (CH_3CH_2); 80.12 ($(CH_3)_3C$); 126.92, 128.61, 129.36, 136.40 (Ph); 155.23 (OCON); 170.24, 170.70, 171.07 (C(1.1), C(1.2), C(4.2)). MS (among others): 873.5 (8), 438

(16), 437 (61), 382 (8), 381 (35), 338 (23), 337 (100), 190 (42), 188 (11), 164 (15), 154 (14), 137 (10), 136 (13), 131 (10), 121 (8), 120 (67), 116 (51), 102 (10), 91 (13), 89 (8). GC: 838 (D-Asp, 0.761%), 844 (L-Asp, 14.189%).

Z-Ala-Leu-OMe (**10a**). As described for **7a**, with Z-Ala-OH (8.3 g, 37 mmol), NMM (4.09 ml, 37 mmol), THF (20 ml), ethyl chloroformate (3.53 ml, 37 mmol), and HCl · H-Leu-OMe (7.09 g, 39 mmol) in THF (80 ml; neutralized with NMM (4.5 ml, 41 mmol) and dissolved with H_2O (5 ml)) for 18 h. FC (100% Et_2O) led to 12.68 g (98%) of **10a** as a weak yellow oil with a D-Leu portion of 2% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*d*, *J* = 6, 2 CH_3(5.2)); 1.38 (*d*, *J* = 7, CH_3(3.1)); 1.40–1.73 (*m*, H–C(4.2), CH_2(3.2)); 3.72 (*s*, MeO); 4.20–4.42, 4.51–4.68 (2*m*, H–C(2.1), H–C(2.2)); 5.10 (*s*, PhCH_2); 5.53 (*d*, *J* = 8, NH(2.1)); 6.68 (*d*, *J* = 7, NH(2.2)); 7.32 (*s*, Ph). ^{13}C-NMR ($CDCl_3$): 18.64 (CH_3(3.1)); 21.85, 22.76 (2 CH_3(5.2)); 24.80 (CH(4.2)); 41.34 (CH_2(3.2)); 50.34, 50.76 (CH(2.1), CH(2.2)); 52.28 (MeO); 66.97 (Ph*C*H_2); 128.00, 128.16, 128.52, 136.22 (*Ph*CH_2); 155.96 (OCON); 172.22, 173.25 (C(1.1), C(1.2)). MS: 352 (20), 351 (62), 307 (19), 236 (7), 217 (12), 183 (7), 146 (15), 134 (19), 92 (19), 91 (100), 88 (7), 86 (26), 70 (7). GC: 475 (D-Leu, *I* = 3604), 528 (L-Leu, *I* = 152523).

Z-Lys(Boc)-Ala-OMe (**11a**). A soln. of Z-Lys(Boc)-OH · $HN(C_6H_{11})_2$ (3.28 g, 8.6 mmol) in THF (30 ml) was cooled to −15° and treated as described for **7a** with ethyl chloroformate (0.64 ml, 6.7 mmol) and HCl · H-Ala-OMe (0.99 g, 7.12 mmol) in THF (30 ml; neutralized with NMM (0.77 ml, 7.0 mmol) and dissolved with H_2O) for 45 h. Recrystallization from hexane/CH_2Cl_2 led to 1.61 g (49%) of **11a** with a m.p. of 60–63° and a D-Ala portion of 2% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.83–0.97 (*m*, CH_2(4.1)); 1.22–1.98 (*m*, CH_2(5.1), CH_2(3.1), CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.00–3.20 (*m*, CH_2(6.1)); 3.73 (*s*, MeO); 4.10–4.26 (*m*, H–C(2.1)); 4.57 (*dq*, *J* = 7.5, 7.5, H–C(2.2)); 4.65–4.75 (*m*, NH(6.1 or 2.1)); 5.10 (*s*, PhCH_2); 5.51 (*d*, *J* = 7.5, NH(6.1 or 2.1)); 6.61 (*d*, *J* = 7.5, NH(2.2)); 7.34 (*s*, Ph). ^{13}C-NMR ($CDCl_3$): 17.90 (CH_3(3.2)); 22.26, 29.45, 32.26, 39.84 (CH_2(3.1), CH_2(4.1), CH_2(5.1), CH_2(6.1)); 28.42 (C(*C*H_3)$_3$C); 48.03, 54.56 (H–C(2.1), H–C(2.2)); 52.44 (MeO); 66.97 (Ph*C*H_2); 79.07 ((CH_3)$_3$*C*); 128.02, 128.13, 128.50, 136.26 (*Ph*CH_2); 156.22, 156.29 (2 OCON); 171.62, 173.21 (C(1.1), C(1.2)). MS (among others): 466 (16), 410 (16), 367 (14), 366 (56), 303 (8), 258 (10), 213 (9), 128 (13), 104 (9), 92 (14), 91 (100), 84 (32), 57 (48). GC: 207 (D-Ala, 0.093%), 224 (L-Ala, 4.698%).

7. *Transesterifications of Peptides. Boc-Gly-Gly-OEt* (**5b**). To a soln. of **5a** (271 mg, 1.1 mmol) and LiBr (478 mg, 5.5 mmol) in EtOH (6 ml), DBU (82 µl, 0.55 mmol) was added at r.t. After 4 h of stirring at r.t., the mixture was worked up according to *Exper. 3*: 192 mg (67%) of **5b** with ≤ 2% of **5a** (^{1}H-NMR). ^{1}H-NMR (80 MHz, $CDCl_3$; crude product): 1.30 (*t*, *J* = 7, CH_3CH$_2$); 1.45 (*s*, *t*-Bu); 3.85, 4.07 (2*d*, *J* = 6, CH_2(2.1), CH_2(2.2)); 4.25 (*q*, *J* = 7, CH_3CH_2); 4.95–5.20 (*m*, NH(2.1)); 6.35–6.65 (*m*, NH(2.2)).

Boc-Gly-Gly-OCHMe$_2$ (**5c**). As described for **5b**, with **5a** (493 mg, 2 mmol), LiBr (869 mg, 10 mmol), Me_2CHOH (10 ml), and DBU (149 µl, 1 mmol) at r.t. over the weekend. FC (5% MeOH/Et_2O) gave 410 mg (75%) of **5c** with ≤ 2% of **5a** (^{1}H-NMR). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.28 (*d*, *J* = 7, (CH_3)$_2$CH); 1.45 (*s*, *t*-Bu); 3.82, 4.02 (2*d*, *J* = 6, CH_2(2.1), CH_2(2.2)); 4.85–5.20 (*m*, (CH$_3$)$_2$C*H*); 5.22–5.55 (*m*, NH(2.1)); 6.60–6.90 (*m*, NH(2.2)).

Boc-Gly-Gly-OCH$_2$Ph (**5d**). As described for **5b**, with **5a** (493 mg, 2 mmol), LiBr (869 mg, 10 mmol), PhCH_2OH (10 ml), and DBU (149 µl, 1 mmol) at r.t. over the weekend. FC (Et_2O) gave 273 mg (42%) of oily **5d** with 7% of **5a** (^{1}H-NMR). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*s*, *t*-Bu); 3.70 (OMe (**5a**), *I* = 3); 3.83, 4.06 (2*d*, *J* = 5.8 and 5.5, resp., CH_2(2.1), CH_2(2.2)); 5.14 (PhCH_2, *I* = 28); 5.51–5.62 (*m*, NH(2.1)); 7.09 (*t*, *J* = 6, NH(2.2)); 7.32 (*s*, *Ph*CH_2).

Z-Gly-Gly-OEt (**6a**). As described for **5b**, with **6a** (589 mg, 2 mmol), LiBr (869 mg, 10 mmol), EtOH (10 ml) and DBU (150 µl, 1 mmol) at r.t. for 66 h. Addition of 1N HCl (2 ml) before workup: 351 mg (60%) of recovered **6a**. ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 1.29 (*t*, *J* = 7.1, CH_3CH$_2$); 4.01 (*s*, PhCH_2); 4.22 (*q*, *J* = 7.1, CH_3CH_2); 4.24, 4.69 (2*s*, CH_2(2.1), CH_2(2.2)); 6.28 (*s*, NH(2.1)); 7.25–7.45 (*m*, NH(2.2), Ph).

Boc-Phe-Ala-OMe (**7a**). a) *At r.t. for 4 d and* b) *At Reflux for 3 h.* To a soln. of **7a** (701 mg, 2 mmol) and LiBr (1.738 g, 20 mmol) in MeOH (10 ml), DBU (0.6 ml, 4 mmol) was added at r.t. After *a*) 4 days of stirring at r.t. or *b*) 3 h reflux, the mixture was treated with 1N HCl (3 ml) and worked up according to *Exper. 3*. *a*) 568 mg (81%) of **7a** with a D-Ala portion of 46% (GC) and a D-Phe portion of 10% (GC); *b*) 479 mg (68%) of **7a** after FC[18]) (AcOEt/hexane 6:4) with a D-Ala portion of 48% (GC) and a D-Phe portion of 28% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$, crude product, identical for *a* and *b*): 1.25, 1.33 (2*d*, *J* = 7, CH_3(3.2), different diastereoisomers); 1.41 (*s*, *t*-Bu); 3.00–3.12 (*m*, CH_2(3.1)); 3.70 (*s*, MeO); 4.26–4.62 (*m*, H–C(2.1), H–C(2.2)); 4.90–5.13 (*m*, NH(2.1)); 6.28, 6.43 (2*d*, *J* = 7, NH(2.2) different diastereoisomers); 7.15–7.38 (*m*, Ph). GC: *a*) 214 (D-Ala, *I* = 10562), 231 (L-Ala, *I* = 12222), 1097 (D-Phe, *I* = 6948), 1119 (L-Phe, *I* = 60970); *b*) 212 (D-Ala, 10.290%), 228 (L-Ala, 11.215%), 1089 (D-Phe, 20.322%), 1112 (L-Phe, 53.421%).

Boc-Phe-Ala-OEt (**7b**). a) *For 6 min and* b) *for 90 min.* To a soln. of **7a** (701 mg, 2 mmol) and LiBr (869 mg, 10 mmol) in EtOH (10 ml), DBU (150 µl, 1 mmol) was added at r.t. After *a*) 6 min or *b*) 90 min, the mixture was

[18]) It was shown, that no diastereoisomer was enriched during FC.

treated with 1N HCl (3 ml) and worked up according to *Exper. 3*: *a*) 700 mg (96%) of **7b** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 4% (GC) and *b*) 705 mg (97%) of **7b** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 16% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): *a*) 1.25 (*t*, *J* = 7.1, CH_3CH_2O); 1.33 (*d*, *J* = 7.2, CH_3(3.2)); 1.39 (*s*, *t*-Bu); 3.06 (*d*, *J* = 6.7, CH_2(3.1)); 3.70 (*s*, MeO (trace of **7a**)); 4.16 (*q*, *J* = 7.1, CH_3CH_2O); 4.29–4.43 (*m*, H–C(2.1)); 4.49 (*dq*, *J* = 7, 7, H–C(2.2)); 5.04 (*d*, *J* = 7, NH(2.1)); 6.52 (*d*, *J* = 7, NH(2.2)); 7.15–7.35 (*m*, Ph); *b*) 1.25 (*t*, *J* = 7, CH_3CH_2O); 1.33 (*d*, *J* = 7, CH_3(3.2)); 1.40 (*s*, *t*-Bu); 3.07 (*d*, *J* = 6, CH_2(3.1)); 3.71 (*s*, MeO (trace of **7a**)); 4.16 (*q*, *J* = 7, CH_3CH_2O); 4.28–4.42 (*m*, H–C(2.1)); 4.49 (*dq*, *J* = 7, 7, H–C(2.2)); 4.95–5.10 (*m*, NH(2.1)); 6.27 (*d*, *J* = 7, NH(2.2, L,D)); 6.52 (*d*, *J* = 7, NH(2.2, L,L)); 7.15–7.35 (*m*, Ph). GC: *a*) 207 (D-Ala, *I* = 1125), 225 (L-Ala, *I* = 25634); *b*) 208 (D-Ala, *I* = 476), 225 (L-Ala, *I* = 2512).

Boc-Phe-Ala-OCHMe$_2$ (**7c**). *For 90 min at r.t. and* a) *LiBr*, b) *LiClO$_4$ and* c) *LiBF$_4$*. To a soln. of **7a** (701 mg, 2 mmol) and *a*) LiBr (869 mg, 10 mmol), *b*) $LiClO_4$ (1.064 g, 10 mmol), and *c*) $LiBF_4$ (937 mg, 10 mmol) in Me_2CHOH (10 ml), DBU (150 µl, 1 mmol) was added at r.t. After 90 min stirring at r.t., the mixture was treated with 1N HCl (3 ml) and worked up according to *Exper. 3*: *a*) 703 mg (93%) of **7c** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 17% (GC); *b*) 709 mg (94%) of **7c** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 26% (GC); *c*) 93% of **7a** (^{1}H-NMR). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): *a*) 1.22, 1.24 (2*d*, *J* = 6.3, $(CH_3)_2CH$); 1.23, 1.33 (2*d*, *J* = 6.2 and 7.2, resp., CH_3(3.2, L,D and L,L)); 1.40 (*s*, *t*-Bu); 3.06 (*d*, *J* = 6.7, CH_2(3.1)); 3.70 (*s*, MeO (trace of **7a**)); 4.28–4.45 (*m*, H–C(2.1)); 4.44 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.28 (*d*, *J* = 7, NH(2.2), L,D); 6.49 (*d*, *J* = 7, NH(2.2), L,L); 7.15–7.35 (*s*, Ph); b) 1.22, 1.24 (2*d*, *J* = 6, $(CH_3)_2CH$); 1.33 (*d*, *J* = 7.2, CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1)); 3.71 (*s*, MeO (trace of **7a**)); 4.28–4.45 (*m*, H–C(2.1)); 4.45 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.12 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.25 (*d*, *J* = 7, NH(2.2), L,D); 6.45 (*d*, *J* = 7, NH(2.2), L,L); 7.15–7.36 (*s*, Ph); *c*) 1.22, 1.26 (2*d*, *J* = 6, little $CH(CH_3)_2$); 1.34 (*d*, *J* = 7.1, CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1), *I* = 18); 3.71 (*s*, MeO, *I* = 24); 4.26–4.45 (*m*, H–C(2.1)); 4.52 (*dq*, *J* = 7, 7, H–C(2.2)); 4.91–5.08 (*m*, trace of $(CH_3)_2CH$, NH(2.1)); 6.42 (*d*, *J* = 7, NH(2.2)); 7.16–7.36 (*s*, Ph).

Boc-Phe-Ala-OCHMe$_2$ (**7c**). a) *With 5 equiv. of LiBr and 0.5 equiv. of DBU at r.t. for 45 min*, b) *with 2 equiv. of LiBr and 0.5 equiv. of DBU at r.t. for 90 min*, c) *with 2 equiv. of LiBr and 2 equiv. of DBU at r.t. for 90 min*, d) *with 5 equiv. of LiBr and 0.5 equiv. of DBU at –10° for 44 h, and* e) *with 5 equiv. of LiBr and 0.5 equiv. of DBU at 0° for 16 h.* To a soln. of **7a** (701 mg, 2 mmol) and LiBr (*a*, *d*, *e*: 869 mg, 10 mmol; *b*, *c*: LiBr (347 mg, 4 mmol)) in Me_2CHOH (10 ml), DBU (*a*, *b*, *d*, *e*: 150 µl, 1 mmol; *c*: 600 µl, 4 mmol) was added at r.t. (*a*, *b*, *c*), –10° (*d*); 0° (*e*). After stirring for *a*) 45 min, *b*), *c*) 90 min, *d*) 44 h, *e*) 16 h at the given temp., the mixture was treated with dil. HCl/Et_2O (3 ml) and worked up according to *Exper. 3*: *a*) 721 mg (95%) of **7c** with 9% of **7a** (^{1}H-NMR) and a D-Ala portion of 8% (GC); *b*) 719 mg (95%) of **7c** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 13% (GC); *c*) 698 mg (92%) of **7c** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 18% (GC); *d*) 664 mg (88%) of **7c** with 4% of **7a** (^{1}H-NMR) and a D-Ala portion of 4% (GC); *e*) 664 mg (88%) of **7c** with ≤ 2% of **7a** (^{1}H-NMR) and a D-Ala portion of 5% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): *a*) 1.22, 1.24 (2*d*, *J* = 6, $(CH_3)_2CH$); 1.33 (*d*, *J* = 7, CH_3(3.2)); 1.40 (*s*, *t*-Bu); 3.06 (*d*, *J* = 7, CH_2(3.1), *I* = 18.5); 3.70 (*s*, MeO (**7a**), *I* = 2.5); 4.28–4.45 (*m*, H–C(2.1)); 4.44 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.27 (*d*, *J* = 7, trace of NH(2.2), L,D); 6.48 (*d*, *J* = 7, NH(2.2), L,L); 7.15–7.35 (*m*, Ph); *b*) 1.22, 1.25 (2*d*, *J* = 6.0 and 6.2, resp., $(CH_3)_2CH$); 1.33 (*d*, *J* = 7.1, CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 6.6, CH_2(3.1)); 3.70 (*s*, MeO (trace of **7a**)); 4.28–4.45 (*m*, H–C(2.1)); 4.45 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.27 (*d*, *J* = 7, little NH(2.2), L,D); 6.47 (*d*, *J* = 7.4, NH(2.2), L,L); 7.15–7.38 (*m*, Ph); *c*) 1.22, 1.24 (2*d*, *J* = 6.0 and 6.2, resp., $(CH_3)_2CH$); 1.33 (*d*, *J* = 7.1, CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 6.6, CH_2(3.1)); 3.70 (*s*, MeO (trace of **7a**)); 4.28–4.45 (*m*, H–C(2.1)); 4.45 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.27 (*d*, *J* = 7, little NH(2.2), L,D); 6.47 (*d*, *J* = 7.4, NH(2.2), L,L); 7.15–7.38 (*m*, Ph); *d*) 1.22, 1.25 (2*d*, *J* = 6.2, $(CH_3)_2CH$); 1.33 (*d*, *J* = 7.1, CH_3(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 6.7, CH_2(3.1), *I* = 15.5); 3.72 (*s*, MeO (**7a**), *I* = 1.0); 4.28–4.45 (*m*, H–C(2.1)); 4.44 (*dq*, *J* = 7.2, 7.2, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.44 (*d*, *J* = 7.8, NH(2.2)); 7.16–7.37 (*m*, Ph); *e*) 1.22, 1.25 (2*d*, *J* = 6, $(CH_3)_2CH$); 1.33 (*d*, *J* = 7, CH_3(3.2)); 1.40 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1)); 3.71 (*s*, MeO (trace of **7a**)); 4.28–4.45 (*m*, H–C(2.1)); 4.44 (*dq*, *J* = 7, 7, H–C(2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.44 (*d*, *J* = 7, NH(2.2)); 7.17–7.36 (*m*, Ph). GC: *a*) 210 (D-Ala, *I* = 1441), 229 (L-Ala, *I* = 15580); *b*) 213 (D-Ala, *I* = 7185), 231 (L-Ala, *I* = 48354); *c*) 210 (D-Ala, *I* = 6996), 228 (L-Ala, *I* = 32442); *d*) 209 (D-Ala, *I* = 1856), 228 (L-Ala, *I* = 43426); *e*) 207 (D-Ala, *I* = 136), 223 (L-Ala, *I* = 2827).

Boc-Phe-Ala-OCH$_2$CH=CH$_2$ (**7d**). As described for **5b**, with **7a** (701 mg, 2 mmol), LiBr (869 mg, 10 mmol), CH_2=$CHCH_2OH$ (10 ml), and DBU (150 µl, 1 mmol) at 0° for 6 h. Addition of dil. HCl/Et_2O (3 ml) before workup: 686 mg (91%) of weak brownish **7d** with 3% of **7a** (^{1}H-NMR) and a D-Ala portion of 5% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 1.36 (*d*, *J* = 7, CH_3(3.2)); 1.40 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1), *I* = 14); 3.70 (*s*, MeO (**7a**), *I* = 0.7); 4.28–4.65 (*m*, H–C(2.1), H–C(2.2), CH_2=$CHCH_2$); 5.01 (*d*, *J* = 7, NH(2.1)); 5.09–5.38 (*m*,

CH_2=$CHCH_2$); 5.78–6.11 (*m*, CH_2=$CHCH_2$); 6.49 (*d*, *J* = 7, NH(2.2)); 7.16–7.37 (*m*, Ph). GC: 214 (D-Ala, *I* = 1162), 231 (L-Ala, *I* = 24430).

Boc-Phe-Ala-OCMe$_3$ (**7e**). As described for **5b**, with **7a** (701 mg, 2 mmol), LiBr (869 mg, 10 mmol), Me_3COH (10 ml) and THF (10 ml), and DBU (150 µl, 1 mmol) at r.t. for 54 h. Addition of 1N HCl (3 ml) before workup: 441 mg of a mixture containing 88% of **7a** and 12% of **7e** (^{1}H-NMR) with a D-Ala portion of *ca.* 46% (^{1}H-NMR). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 1.24 (*d*, *J* = 7.2, CH_3(3.2, L,D)); 1.34 (*d*, *J* = 7.2, CH_3(3.2), L,L); 1.40 (*s*, *t*-BuOCO); 1.43 (*t*-BuO (**7e**)); 3.05, 3.06 (2*d*, *J* = 6.9 and 6.6, resp., CH_2 (3.1), L,D and L,L, *I* = 25); 3.71 (*s*, MeO (**7a**), *I* = 33); 4.25–4.42, 4.42–4.60 (2*m*, H–C(2.1), H–C(2.2)); 4.95–5.13 (*m*, NH(2.1)); 6.25 (*d*, *J* = 6, NH(2.2, L,D), *I* = 5); 6.42 (*d*, *J* = 6, NH(2.2), L,L, *I* = 6); 7.16–7.35 (*m*, Ph).

Boc-Phe-Leu-OMe (**8a**). a) *At 25° and* b) *at 3°*. To a soln. of **8b** (937 mg, 2 mmol), LiBr (868 mg, 10 mmol) in MeOH (10 ml), DBU (150 µl, 1 mmol) was added at *a*) r.t.; *b*) 3°. After *a*) 20 h; *b*) 21 h of stirring at the given temp., the mixture was worked up, after addition of dil. HCl/Et_2O (2 ml) according to *Exper. 3*: *a*) 707 mg (90%) of **8a** with ⩽ 2% of **8b** (^{1}H-NMR) and a D-Leu portion of 31% (GC) after drying under h.v. for several days; *b*) 739 mg of **8a** with ⩽ 2% of **8b** and a $PhCH_2OH$ portion of 39% (^{1}H-NMR) and a D-Leu portion of 6% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): *a*) 0.80–0.95 (*m*, 2 CH_3(5.2)); 1.30–1.75 (*m*, H–C(4.2), CH_2(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1)); 3.68, 3.69 (2*s*, MeO, L,L and L,D); 4.25–4.45, 4.45–4.65 (2*m*, H–C(2.1), H–C(2.2)); 4.95–5.05 (*m*, NH(2.1)); 5.12 (*s*, $PhCH_2O$ (trace of **8b**)); 6.12–6.29 (*m*, NH(2.2)); 7.17–7.37 (*m*, Ph); *b*) 0.80–0.98 (*m*, 2 CH_3(5.2)); 1.30–1.85 (*m*, H–C(4.2), CH_2(3.2)); 1.41 (*s*, *t*-Bu); 3.07 (*d*, *J* = 7, CH_2(3.1)); 3.69, 3.72 (2*s*, MeO, L,L and little L,D); 4.25–4.45, 4.47–4.65 (2*m*, H–C(2.1), H–C(2.2)); 4.70 (*s*, $PhCH_2OH$, *I* = 9); 4.95–5.08 (*m*, NH(2.1)); 6.25 (*d*, *J* = 7, NH(2.2)); 7.17–7.43 (*m*, Ph, $PhCH_2OH$). GC: *a*) 466 (D-Leu, *I* = 7014), 508 (L-Leu, *I* = 15510); *b*) 460 (D-Leu, 0.862%), 504 (L-Leu, 13.425%).

Boc-Phe-Leu-OCH$_2$Ph (**8b**). As described for **5b**, with **8a** (785 mg, 2 mmol), LiBr (869 mg, 10 mmol), $PhCH_2OH$ (10 ml), and DBU (150 µl, 1 mmol) at 3° for 7 days. Addition of dil. HCl/Et_2O (2 ml) before workup followed by removal of $PhCH_2OH$ at 70°/h.v. led to 825 mg (88%) of **8b**, after recrystallization from hexane (and little AcOEt). Prior to recrystallization, crude **8b** contained 6% of **8a** (^{1}H-NMR) and a D-Leu portion of 27% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; prior to recrystallization): 0.74–0.98 (*m*, 2 CH_3(5.2), *I* = 63); 1.40 (*s*, *t*-Bu); 1.30–1.72 (*m*, H–C(4.2), CH_2(3.2)); 3.04 (*d*, *J* = 6, CH_2(3.1)); 3.69 (*s*, MeO (**8a**), *I* = 1.8); 4.29–4.50, 4.50–4.70 (2*m*, H–C(2.1), H–C(2.2)); 5.12 (*s*, $PhCH_2O$); 5.12–5.30 (*m*, NH(2.1)); 6.4–6.55 (*m*, NH(2.2)); 7.12–7.44 (*m*, 2 Ph). GC: 467 (D-Leu, 10.240%), 512 (L-Leu, 27.832%).

Boc-Phe-Leu-OEt (**8c**). As described for **5b**, with **8a** (785 mg, 2 mmol), LiBr (869 mg, 10 mmol), EtOH (10 ml), and DBU (150 µl), at r.t. for 6 min. Addition of dil. HCl/Et_2O (2 ml) before workup: 786 mg (97%) of **8c** with 7% of **8a** (^{1}H-NMR) and containing its D-Leu isomer to 3% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.89, 0.91 (2*d*, *J* = 6, CH_3(5.2)); 1.23 (*t*, *J* = 7, CH_3CH_2); 1.41 (*s*, *t*-Bu); 1.46–1.62 (*m*, H–C(4.2), CH_2(3.2)); 3.07 (*d*, *J* = 7, CH_2(3.1), *I* = 21.5); 3.69 (*s*, MeO (**8a**), *I* = 2.3); 4.14 (*q*, *J* = 7, CH_3CH_2); 4.34 (*td*, *J* = 7, 7, H–C(2.1 or 2.2)); 4.48–4.61 (*m*, H–C(2.1 or 2.2)); 4.92–5.08 (*m*, NH(2.1); 6.28 (*d*, *J* = 8, NH(2.2)); 7.17–7.35 (*m*, Ph). GC: 469 (D-Leu, *I* = 16108), 517 (L-Leu, *I* = 492351).

Boc-Phe-Leu-OCHMe$_2$ (**8d**). As described for **5b**, with **8a** (785 mg, 2 mmol), LiBr (869 mg, 10 mmol), Me_2CHOH (10 ml), and DBU (150 µl, 1 mmol) at r.t. for 90 min. Addition of dil. HCl/Et_2O (2 ml) before workup: 779 mg (93%) of **8d** with 4% of **8a** (^{1}H-NMR) and containing its D-Leu isomer to 13% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.89, 0.91 (2*d*, *J* = 6, CH_3(5.2)); 1.23 (*t*, *J* = 7, $(CH_3)_2CH$); 1.41 (*s*, *t*-Bu); 1.46–1.62 (*m*, H–C(4.2), CH_2(3.2)); 3.07 (*d*, *J* = 7, CH_2(3.1), *I* = 22.5); 3.69 (*s*, MeO (**8a**), *I* = 1.0); 4.34 (*td*, *J* = 7, 7, H–C(2.1 or 2.2)); 4.42–4.58 (*m*, H–C(2.1 or 2.2)); 4.91–5.10 (*m*, $(CH_3)_2CH$, NH(2.1)); 6.18 (*d*, *J* = 8, NH(2.2), little L,D)); 6.29 (*d*, *J* = 8, NH(2.2), L,L); 7.17–7.37 (*m*, Ph). GC: 462 (D-Leu, *I* = 19723), 505 (L-Leu, *I* = 137492).

Boc-Phe-Asp(OMe)-OMe (**9b**). As described for **5b**, with **9a**, (218 mg, 0.5 mmol), LiBr (218 mg, 2.5 mmol), MeOH (3 ml), and DBU (36 µl, 0.25 mmol) at 0° for 30 min. Addition of 1N HCl (2 ml) before workup: 191 mg (94%) of **9b** with 4% of **9a** (^{1}H-NMR) and a D-Asp portion of 15% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 1.19–1.30 (*m*, 2 CH_3CH_2 (**9a**), *I* = 3.5); 1.41 (*s*, *t*-Bu); 2.82, 3.01 (2*dd*, *J* = 4.4, 17.3, 2 H–C(3.2)); 3.08 (*d*, *J* = 6.3, CH_2(3.1)); 3.66, 3.73 (2*s*, 2 MeO, *I* = 92); 4.05–4.22 (*m*, CH_3CH_2 (**9a**)); 4.30–4.48 (*m*, H–C(2.1 or 2.2)); 4.79 (*dt*, *J* = 4.8, 7.7, H–C(2.1 or 2.2)); 4.87–5.00 (*m*, NH(2.1)); 6.83 (*d*, *J* = 7.1, NH(2.2)); 7.18–7.34 (*m*, Ph). GC: 833 (D-Asp, 3.633%), 840 (L-Asp, 19.926%).

Z-Ala-Leu-OMe (**10a**). As described for **5b**, with **10a** (701 mg, 2 mmol), LiBr (869 mg, 10 mmol), MeOH (10 ml), and DBU (150 µl, 1 mmol) at r.t. for 20 h. Addition of 1N HCl (2 ml) before workup: 508 mg (73%) of a still slightly impure, oily **10a** after FC (hexane/AcOEt 4:6). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.8–1.0 (*m*, 2 CH_3(5.2)); 1.18–1.75 (*m*, H–C(4.2), CH_2(3.2), impurity); 1.38 (*d*, *J* = 7, CH_3(3.1)); 2.25–2.38 (*m*, weak impurity); 3.70, 3.71 (2*s*, MeO, L,L and L,D); 3.98 (*d*, *J* = 5, weak impurity); 4.02–4.40, 4.52–4.78 (2*m*, H–C(2.1), H–C(2.2)); 5.10 (*s*, $PhCH_2$); 5.53, 5.55 (2*d*, *J* = 8, NH(2.1), L,L and L,D); 6.62, 6.75 (2*d*, *J* = 8, NH(2.2), L,L and L,D); 7.33 (*s*, Ph).

Z-Ala-Leu-OEt (**10b**). As described for **5b**, with **10a** (701 mg, 2 mmol), LiBr (869 mg, 10 mmol), EtOH (10 ml), and DBU (150 µl, 1 mmol) at r.t. for 6 min (→brownish red). Addition of dil. HCl/Et_2O (4 ml) before workup: 679 mg (93%) of a slightly yellow oil of **10b** with 10% of **10a** (^{1}H-NMR) and a D-Leu portion of 3% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.90 (*d*, $J = 6$, 2 CH_3(5.2)); 1.25 (*t*, $J = 7$, CH_3CH_2); 1.36 (*d*, $J = 7$, CH_3(3.1)); 1.40–1.76 (*m*, H–C(4.2), CH_2(3.2)); 3.71 (*s*, MeO (**10a**), $I = 3$); 4.15 (*q*, $J = 7$, CH_3CH_2); 4.25–4.49, 4.50–4.66 (2*m*, H–C(2.1), H–C(2.2)); 5.09 (*s*, $PhCH_2$, $I = 17$); 5.88 (*d*, $J = 8$, NH(2.1)); 7.02 (*d*, $J = 8$, NH(2.2)); 7.32 (*s*, Ph). GC: 464 (D-Leu, 1.882%), 517 (L-Leu, 56.392%).

Z-Ala-Leu-OCHMe$_2$ (**10c**). As described for **5b**, with **10a** (701 mg, 2 mmol), LiBr (869 mg, 10 mmol), Me_2CHOH (10 ml), and DBU (150 µl, 1 mmol) for 90 min at r.t. Addition of dil. HCl/Et_2O (3 ml) before workup: 645 mg (85%) of a slightly yellow oil of **10c** with 5% of **10a** (^{1}H-NMR) and a D-Leu portion of 9% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.89 (*d*, $J = 6$, 2 CH_3(5.2), $I = 55$); 1.22, 1.24 (2*d*, $J = 6$, $(CH_3)_2CH$); 1.36 (*d*, $J = 7$, CH_3(3.1)); 1.43–1.75 (*m*, H–C(4.2), CH_2(3.2)); 3.69 (*s*, MeO (**10a**), $I = 1.5$); 3.96–4.71 (*m*, H–C(2.1), H–C(2.2)); 4.90–5.12 (*m*, $(CH_3)_2CH$); 5.09 (*s*, $PhCH_2$); 6.04 (*d*, $J = 8$, NH(2.1)); 7.13 (*d*, $J = 8$, NH(2.2)); 7.32 (*s*, Ph). GC: 468 (D-Leu, $I = 18749$), 515 (L-Leu, $I = 196739$).

Z-Lys(Boc)-Ala-OCH$_2$CH=CH$_2$ (**11b**). As described for **5b**, with **11a** (466 mg, 1 mmol), LiBr (434 mg, 5 mmol), CH_2=$CHCH_2OH$ (5 ml), and DBU (74 µl, 0.5 mmol) at 0° for 22 h. Addition of 1N HCl (2 ml) before workup: 458 mg (93%) of **11b** with 3% of **11a** (^{1}H-NMR) and a D-Ala portion of 15% (GC). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.82–0.98 (*m*, CH_2(4.1)); 1.20–1.59 (*m*, CH_2(5.1), CH_3(3.2)); 1.41 (*s*, *t*-Bu); 1.60–1.76, 1.76–1.96 (2*m*, 2 H–C(3.1)); 2.99–3.18 (*m*, CH_2(6.1)); 3.73 (*s*, MeO (**11a**), $I = 10$); 4.10–4.27, 4.48–4.78 (2*m*, H–C(2.1), H–C(2.2), CH_2=$CHCH_2$, NH(6.1 or 2.1)); 5.09 (*s*, $PhCH_2$); 5.20–5.39 (*m*, CH_2=$CHCH_2$); 5.54 (*d*, $J = 7$, NH(6.1 or 2.1)); 5.79–6.01 (*m*, CH_2=$CHCH_2$, $I = 95$); 6.69 (*d*, $J = 7$, NH(2.2)); 7.34 (*s*, Ph). GC: 212 (D-Ala, $I = 66673$), 231 (L-Ala, $I = 388281$).

Boc-Ala-Sar-MeLeu-OMe (**12b**). As described for **5b**, with Boc-Ala-Sar-MeLeu-OCH_2Ph (**12a**; 478 mg, 1 mmol), LiBr (435 mg, 5 mmol), MeOH (5 ml), and DBU (75 µl, 0.5 mmol) at 3° for 50 h. Addition of 1N HCl (2 ml) before workup: 365 mg of $PhCH_2OH$-containing **12b** (< 91%) with ≤ 2% of **12a** (^{1}H-NMR). ^{1}H-NMR (200 MHz, $CDCl_3$; crude product): 0.85–1.03 (*m*, 2 CH_3(5.3)); 1.16–1.30 (*m*, H–C(4.3)); 1.34, 1.35 (2*d*, $J = 6.9$, CH_3(3.1), different conformations); 1.42 (*s*, *t*-Bu); 1.65–1.83 (*m*, CH_2(3.3)); 2.86, 3.06, 3.07 (3*s*, CH_3–N(2.2), CH_3–N(2.3), major conformation); 2.79, 2.88, 2.91, 2.94 (4*s*, CH_3–N(2.2), CH_3–N(2.3), minor conformation); 3.65 (*s*, MeO, major conformation); 3.69 (*s*, MeO, minor conformation); 3.77–4.15, 4.30–4.46, 4.46–4.75 (3*m*, H–C(2.1), CH_2(2.2) and minor conformations); 5.22 (*dd*, $J = 9, 6$, H–C(2.3)); 5.40–5.55 (*m*, NH(2.1)); 7.23–7.40 (*m*, $PhCH_2OH$).

Z-Arg-Lys(Z)-Asp(OMe)-Val-Tyr-OMe · HCl (**13b**). Addition of Z-Arg-Lys(Z)-Asp(OCH_2Ph)-Val-Tyr-OCH_2Ph · HCl (**13a**; 1.165 g, 1 mmol) and LiBr (435 mg, 5 mmol) to MeOH (5 ml) led to a suspension, which could be dissolved upon further addition of LiBr (435 mg, 5 mmol) in THF (10 ml). After cooling to 3°, DBU (225 µl, 1.5 mmol) was added. After 24 h stirring at 3°, the mixture was treated with 1N HCl (100 ml), and **13b** was filtered. The filtered solid was recrystallized from MeOH (with little H_2O): 963 mg (89%) of **13b** with ≤ 5% of **13a** (^{1}H-NMR) and a D-Tyr portion of 3% (GC, prior to recrystallization), after 5 days of drying under h.v. ^{1}H-NMR (200 MHz, DMSO): 0.70–0.85 (*m*, 2 CH_3(4.4)); 1.10–1.78, 1.82–2.06, 2.55–3.15 (3*m*); 3.35 (*s*, H_2O); 3.51, 3.53, 3.54 (3*s*, MeO, several conformations); 3.93–4.11, 4.11–4.42, 4.53–4.80 (3*m*); 4.95–5.10 (*m*, NH(2.1), NH(6.2)); 6.65, 6.99 (2*d*, $J = 8$, 2 NH); 7.15–7.68 (*m*, NH); 7.33 (*s*, Ph); 7.78 (*d*, $J = 8$, NH); 7.85–8.08, 8.32–8.50 (2*m*, NH); 9.26 (*s*). GC: 1320 (D-Tyr, $I = 419$), 1338 (L-Tyr, $I = 14173$).

Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OEt (**14b**). As described for **5b**, with Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OEt (**14a**; 143 mg, 0.2 mmol), LiBr (87 mg, 1 mmol), EtOH (2 ml), and DBU (15 µl, 0.1 mmol) at 0° for 1 h. Addition of dil. HCl/Et_2O (4 ml) before workup: 167 mg of a colorless oil of **14b** with ≤ 5% of **14a** (crude ^{1}H-NMR) and a D-Ala portion of 3% (crude GC). FC ($MeOH/CH_2Cl_2$ 3:97) yielded 138 mg (95%) of **14b**. ^{1}H-NMR (200 MHz, $CDCl_3$; after FC): 0.70–1.20 (*m*, CH_3(4.1), CH_3(5.3), CH_3(4.4), CH_3(5.5)); 1.1–2.40 (*m*, aliph. H's); 1.24 (*t*, $J = 7$, CH_3CH_2O); 1.32 (*d*, $J = 7$, CH_3(3.6)); 2.73–2.85, 2.85–3.12, 3.12–3.39 (3*m*, CH_3–N(2.2), CH_3–N(2.3), CH_3–N(2.5)); 3.83–3.40 (*m*); 4.16 (*q*, $J = 7$, CH_3CH_2O); 4.28–4.95, 4.95–5.30 (2*m*, H–C(2.1), CH_2(2.2), H–C(2.3), H–C(2.4), H–C(2.5), H–C(2.6)); 5.57 (*d*, $J = 8$, NH(2.1)); 5.96, 6.50, 6.61, 6.74, 7.22, 7.75, 7.83, 7.93, 8.32 (9*d*, $J = 7$–8, NH, different conformations). GC: 215 (D-Ala, $I = 18960$), 236 (L-Ala, $I = 643859$).

8. *Peptide-Resin Cleavages. Boc-Leu-Ala-Gly-Val-OMe* (**15b**). Boc-Leu-Ala-Gly-Val-(PAM resin)[19] (**15a**; 300 mg, 0.168 mmol of peptide) was suspended in 3 ml of a 0.28M LiBr/MeOH soln. (487 mg of LiBr/20 ml of MeOH) and stirred at r.t. for 15 min. DBU (50 µl, 0.34 mmol) was added, and after 4 h stirring at r.t., the mixture was

[19]) Loading, 0.559 mmol · g^{-1}.

filtered, the resin washed with AcOEt (*ca.* 10 ml), treated with 1N HCl (*ca.* 10 ml), and extracted twice with AcOEt (*ca.* 10 ml). The combined org. extract was dried ($MgSO_4$) and evaporated and the residue dried under h.v.: 78 mg of slightly impure **15b** with a D-Val portion of 1% (GC). Further purification by FC (5% MeOH/Et_2O) led, after 24 h drying under h.v., to 66 mg (83%) of **15b**. White powder. M.p. 71–72°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91, 0.95 (2*d*, J = 6.4 and 6.7, resp. 2 CH_3(5.1), 2 CH_3(4.4)); 1.24–1.86 (*m*, H–C(4.1), CH_2(3.1)); 1.40 (*d*, J = 7.1, CH_3(3.2)); 1.43 (*s*, *t*-Bu); 2.10–2.23 (*m*, H–C(3.4)); 3.73 (*s*, MeO); 4.01–4.13, 4.13–4.30, 4.49–4.58, 4.58–4.69 (4*m*, H–C(2.1), H–C(2.2), CH_2(2.3), H–C(2.4)); 5.41 (br. *s*, NH(2.1)); 7.22 (*d*, J = 6.0, NH); 7.29 (*d*, NH); 7.44 (*d*, J = 9.4, NH, minor conformation); 7.66 (br. *s*, NH); 8.40–8.52 (*m*, NH, minor conformation). ^{13}C-NMR ($CDCl_3$): 18.02, 18.51, 18.97, 21.92, 22.99, 24.74, 28.33, 31.13, 41.39, 43.22, 49.09, 52.14, 53.42, 57.45, 80.11, 155.99, 169.01, 172.31, 172.96, 172.98 (and some very small peaks). MS: 495 (9, $[M + 23]^+$), 474 (10), 473 (37, $[M + 1]^+$), 417 (14), 374 (12), 373 (54), 286 (16), 260 (14), 242 (9), 229 (20), 190 (9), 189 (80), 185 (17), 157 (10), 154 (9), 149 (18), 137 (9), 136 (12), 132 (41), 130 (23), 129 (20), 107 (10), 91 (9), 89 (10), 86 (68), 77 (11), 74 (10), 73 (24), 72 (55), 71 (17), 70 (10), 69 (15), 57 (100), 56 (10), 55 (29). GC: 289 (D-Val, 0.309%), 306 (L-Val, 24.105%).

Boc-Leu-Ala-Gly-Val-OH (**15c**). The suspension of **15a**[20]) (150 mg, 0.093 mmol of peptide) in a soln. of LiBr (40 mg, 0.46 mmol) in THF (1.8 ml) and H_2O (0.2 ml) was stirred for 15 min at r.t. DBU (7 µl, 0.047 mmol) was added, and after 4 h of stirring at r.t., the mixture was filtered, the resin washed with AcOEt (*ca.* 10 ml), treated with 1N HCl (*ca.* 10 ml), and extracted twice with AcOEt (*ca.* 10 ml). The combined org. extract was dried ($MgSO_4$) and evaporated and the residue dried under h.v.: 81 mg of slightly impure **15c** with a D-Val portion of 1% (GC). The yield was determined by ^{1}H-NMR of the crude product with MeCN as internal standard: 34 mg (81%). ^{1}H-NMR (CD_3OD, 10.4 mg of MeCN): 0.86–1.00 (*m*, 2 CH_3(5.1) of **15c**, 2 CH_3(4.4) of **15c**, I = 33); 2.04 (*s*, MeCN, I = 28). GC (**15c**): 303 (D-Val, 0.087%), 322 (L-Val, 11.058%).

Esterification of the crude product with CH_2N_2 led to a compound with ^{1}H-NMR spectra corresponding to that of **15b**.

Boc-Leu-Ala-Gly-Val-OEt (**15d**). The suspension of **15a**[20]) (220 mg, 0.136 mmol of peptide) in EtOH (1 ml) and $Ti(OEt)_4$ (1 ml) was refluxed for 7 h and stirred overnight at r.t. The mixture was filtered, the resin washed with AcOEt (*ca.* 10 ml), treated with 1N HCl (*ca.* 10 ml), filtered, and extracted according to *Exper. 3* (half amount of solvent; D-Val portion: ≤ 1% (GC)). FC (10% MeOH/Et_2O) and drying under h.v. gave 52 mg (78%) of **15d**. M.p. 62–63°. White powder. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.75–1.00 (*m*, 2 CH_3(5.1), 2 CH_3(4.4)); 1.25 (*t*, J = 7.1, CH_3CH_2O); 1.39 (*d*, J = 7, CH_3(3.2)); 1.40 (*s*, *t*-Bu); 1.40–1.75 (*m*, H–C(4.1), CH_2(3.1)); 2.05–2.28 (*m*, H–C(3.4)); 3.92–4.28, 4.43–4.70 (2*m*, CH_3CH_2O, H–C(2.1), H–C(2.2), CH_2(2.3), H–C(2.4)); 5.44 (*d*, J = 7.9, NH(2.1)); 7.15–7.35, 7.55–7.70 (2*m*, NH(2.2), NH(2.3), NH(2.4)). ^{13}C-NMR ($CDCl_3$): 14.27, 14.36, 18.00, 18.09, 18.67, 19.10, 21.95, 22.05, 23.15, 24.90, 28.50, 31.40, 41.59, 43.44, 49.23, 53.62, 57.56, 61.45, 80.29, 156.32, 169.25, 172.19, 173.28. MS: 487.5 (18, $[M + 1]^+$), 431.4 (7), 387.4 (15), 286 (9), 229 (11), 203 (36), 185 (9), 157 (8), 154 (12), 149 (34), 147 (17), 146 (23), 137 (15), 136 (17), 133 (9), 130 (13), 129 (20), 123 (10), 121 (8), 119 (12), 113 (10), 111 (11), 109 (16), 107 (13), 105 (14), 97 (20), 95 (27), 93 (13), 91 (21), 86 (28), 85 (17), 83 (30), 81 (31), 79 (17), 77 (16), 73 (39), 72 (35), 71 (43), 70 (11), 69 (58), 67 (27), 57 (100), 56 (11), 55 (79). GC (prior to FC): 293 (D-Val, 0.067%), 309 (L-Val, 23.357%).

Boc-Leu-Ala-Gly-Phe-OMe (**16b**). *At r.t. for 4 h.* To the suspension of Boc-Leu-Ala-Gly-Phe-(PAM resin)[19]) (**16a**; 150 mg, 0.084 mmol of peptide) in a soln. of LiBr (36 mg, 0.41 mmol) in MeOH (2 ml), DBU (6.3 µl, 0.042 mmol) was added after 15 min of stirring at r.t. After 4 h stirring at r.t., the mixture was filtered, the resin washed with AcOEt (*ca.* 10 ml), treated with 1N HCl (*ca.* 10 ml) and worked up according to *Exper. 3* (half amount of solvent): 58 mg of a colorless oil of **16b** with a D-Phe portion of 14% (GC). The content of **16b** was determined by ^{1}H-NMR of the crude product with MeCN as internal standard: 43 mg (98%). ^{1}H-NMR (CD_3OD, 8.2 mg of MeCN): 0.80–1.00 (*m*, 2 CH_3(5.1) from **16b**), I = 47); 2.00 (*s*, MeCN, I = 57). Further purification by FC (5% MeOH/Et_2O) led, after 24 h of drying under h.v., to 42 mg (96%) of **16b**. White powder. M.p. 71–73°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91, 0.93 (2*d*, J = 6.4, 2 CH_3(5.1)); 1.37 (*d*, J = 7.1, CH_3(3.2)); 1.43 (*s*, *t*-Bu); 1.45–1.53 (*m*, H–C(4.1)); 1.57–1.74 (*m*, CH_2(3.1)); 3.05–3.17 (*m*, CH_2(3.4)); 3.69 (*s*, MeO); 3.93 (*d*, J = 5.6, CH_2(2.3)); 4.05–4.17 (*m*, H–C(2.1) or H–C(2.4)); 4.46 (*dq*, J = 7, 7, H–C(2.2)); 4.83 (*dt*, J = 6,8, H–C(2.1) or H–C(2.4)); 5.11 (*d*, J = 7.1, NH(2.1)); 6.84, 6.93 (2*d*, J = 7.0 and 7.8, resp. NH(2.2), NH(2.3) or NH(2.4)); 7.10–7.30 (*m*, 1 NH, Ph). ^{13}C-NMR ($CDCl_3$): 18.16, 21.88, 22.99, 24.74, 28.32, 37.92, 41.16, 43.04, 49.13, 52.31, 53.46, 80.29, 127.05, 128.54, 129.25, 136.03, 156.03, 168.56, 171.88, 172.64, 172.95. MS: 543 (6, $[M + 23]^+$), 521 (7, $[M + 1]^+$), 422 (6), 421 (20), 308 (9), 286 (13), 242 (9), 238 (15), 237 (75), 229 (23), 185 (15), 181 (12), 180 (65), 162 (6), 158 (5), 136 (5), 133 (11), 132 (5), 131 (9), 130 (22), 129 (7), 128 (7), 121 (12), 120 (61), 119 (7), 118 (5), 103 (5), 100 (6), 99 (5), 98 (7), 91 (14),

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[20]) Loading, 0.617 mol · g^{-1}.

89 (6), 88 (10), 87 (7), 86 (72), 85 (7), 84 (8), 77 (7), 74 (10), 70 (10), 69 (7), 58 (7), 57 (100), 56 (9), 55 (13). GC: 1102 (D-Phe, 3.182%), 1125 (L-Phe, 19.211%).

At 0° for 8 h. As described above, but at 0° for 8 h: 64 mg of a colorless oil of **16b** with a D-Phe portion of 2% (GC). The content of **16b** was determined by ^{1}H-NMR of the crude product with MeCN as internal standard: 38 mg (86%). ^{1}H-NMR (CD_3OD, 9.1 mg of MeCN): 0.85–0.98 (*m*, 2 CH_3(5.1) of **16b**, I = 45.5); 2.02 (*s*, MeCN, I = 69.5). Further purification by FC (10% MeOH/Et_2O) led, after 24 h of drying under h.v., to 36 mg (82%) of **16b**. White powder. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90, 0.91 (2*d*, J = 6, 2 CH_3(5.1)); 1.37 (*d*, J = 7, CH_3(3.2)); 1.42 (*s*, *t*-Bu); 1.45–1.75 (*m*, H–C(4.1), CH_2(3.1)); 3.00–3.20 (*m*, CH_2(3.4)); 3.69 (*s*, MeO); 3.93 (*d*, J = 6, CH_2(2.3)); 4.03–4.18 (*m*, H–C(2.1) or H–C(2.4)); 4.48 (*dq*, J = 7, 7, H–C(2.2)); 4.83 (*dt*, J = 6, 8, H–C(2.1) or H–C(2.4)); 5.20 (*d*, J = 7.1, NH(2.1)); 6.93, 7.03 (2*d*, J = 7 and 8, resp., NH(2.2), NH(2.3) or NH(2.4)); 7.09–7.38 (*m*, 1 NH, Ph). GC: 1056 (D-Phe, 0.534%), 1078 (L-Phe, 24.579%).

Boc-Leu-Ala-Gly-Phe-OH (**16c**). As described for **16b** (r.t., 4 h), but with THF/10% H_2O (2 ml) instead of MeOH. For workup, the HCl-treated resin was extracted twice with AcOEt (*ca.* 10 ml), the combined org. extract dried ($MgSO_4$) and evaporated, and the residue dried under h.v.: 96 mg of impure **16c** with a D-Phe portion of 2% (GC). The content of **16c** was determined by ^{1}H-NMR of the crude product with MeCN as internal standard: 40 mg (93%). ^{1}H-NMR (CD_3OD, 4.0 mg of MeCN): 0.80–0.98 (*m*, 2 CH_3(5.1) of **16c**, I = 37.5); 2.02 (*s*, MeCN, I = 23.0). GC (**16c**): 1087 (D-Phe, 0.597%), 1109 (L-Phe, 37.209%).

The esterification of the crude product with CH_2N_2 led to a compound with ^{1}H-NMR spectra corresponding to **16b**.

Boc-Leu-Ala-Gly-Phe-OEt (**16d**). The suspension of **16a**[19]) (160 mg, 0.089 mmol of peptide) in EtOH (1 ml) and $Ti(OEt)_4$ (1 ml) was refluxed for 8 h and stirred at r.t. overnight. The mixture was filtered and the resin washed with AcOEt (*ca.* 10 ml), treated with 1N HCl (*ca.* 10 ml), filtered, and extracted according to *Exper. 3* (half amount of solvent; D-Phe portion: 1% (GC)). Further purification by FC (10% MeOH/Et_2O) and drying under h.v. led to 45 mg (94%) of **16d**. White solid. M.p. 74–75°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90, 0.91 (2*d*, J = 6.2, 2 CH_3(5.1)); 1.15–1.75 (*m*, H–C(4.1), CH_2(3.1)); 1.19 (*t*, J = 7.2, CH_3CH_2O); 1.36 (*d*, J = 7.1, CH_3(3.2)); 3.00–3.20 (*m*, CH_2(3.4)); 3.95 (*d*, J = 5.4, CH_2(2.3)); 4.02–4.20 (*m*, 1 H, H–C(2.1, 2.2, or 2.4)); 4.12 (*q*, J = 7.2, CH_3CH_2O); 4.40–4.60, 4.75–4.89 (2*m*, 2 H, H–C(2.1, 2.2, or 2.4)); 5.20 (*d*, J = 7.3, NH(2.1)); 5.55 (d, J = 7, NH(2.1), minor conformation); 6.97, 7.01 (2*d*, J = 7, 2 H, NH(2.2, 2.3, or 2.4)); 7.08–7.40 (*m*, 6 H, NH(2.2, 2.3, or 2.4), Ph). ^{13}C-NMR ($CDCl_3$): 14.22, 18.30, 22.03, 23.17, 24.86, 24.92, 28.50, 38.20, 41.34, 43.24, 49.34, 53.69, 61.72, 127.35, 128.83, 129.66, 136.39, 156.35, 168.87, 171.82, 172.99, 173.31. MS: 557.5 (21), 536.5 (10), 535.5 (31), 507.5 (7), 479.5 (9), 436.5 (8), 435.5 (28), 322 (8), 286 (12), 252 (11), 251 (66), 242 (7), 229 (19), 195 (9), 194 (59), 186 (8), 185 (11), 177 (12), 158 (16), 157 (8), 155 (7), 154 (22), 149 (9), 138 (11), 137 (17), 136 (21), 131 (8), 130 (21), 121 (12), 120 (65), 119 (10), 109 (8), 107 (15), 105 (12), 97 (11), 95 (15), 91 (24), 89 (13), 86 (50), 83 (15), 81 (16), 79 (13), 77 (21), 71 (15), 69 (29), 67 (17), 57 (100). GC: 1089 (D-Phe, 0.262%), 1111 (L-Phe, 28.012%).

REFERENCES

[1] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.

[2] C. P. Schickli, ETH-Dissertation 1990, Nr. 9332; C. P. Schickli, D. Seebach, *Liebigs Ann. Chem.* **1991**, in press; D. Seebach, H. M. Bürger, C. P. Schickli, *ibid.* **1991**, in press.

[3] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183; M. W. Rathke, M. Nowak, *J. Org. Chem.* **1985**, *50*, 2624; T. Rosen, C. H. Heathcock, *J. Am. Chem. Soc.* **1985**, *107*, 3731; O. Tsuge, S. Kanemasa, M. Yoshioka, *J. Org. Chem.* **1988**, *53*, 1384; S. Kanemasa, O. Uchida, E. Wada, *ibid.* **1990**, *55*, 4411.

[4] H. Pielartzik, B. Irmisch-Pielartzik, T. Eicher, in 'Methoden der organischen Chemie (Houben-Weyl)', Ed. J. Falbe, G. Thieme Verlag, Stuttgart, 1985, Vol. E5, p. 702.

[5] J. Koskikallio, in 'The Chemistry of Carboxylic Acids and Esters', Ed. S. Patai, Interscience-Publishers (J. Wiley & Sons Ltd.), London, 1969, Chapt. 3, p. 103.

[6] D. Seebach, *Angew. Chem.* **1990**, *102*, 1363; *ibid. Int. Ed.* **1990**, *29*, 1320.

[7] D. Seebach, B. Weidmann, L. Widler, in 'Modern Synthetic Methods 1983; Transition Metals in Organic Chemistry', Ed. R. Scheffold, O. Salle Verlag, Frankfurt, 1983, Vol. 3, p. 312.

[8] W. Pereira, V. Close, W. Patton, B. Halpern, *J. Org. Chem.* **1969**, *34*, 2032.

[9] B. Lejczak, P. Kafarski, J. Szewczyk, *Synthesis* **1982**, 412.

[10] J. Otera, S. Ioka, H. Nozaki, *J. Org. Chem.* **1989**, *54*, 4013.

[11] M.J. Green, Eur.-Pat. 0110629, 17th Nov. 1983 (*CA:* **1984**, *101*, 170717k); M.J. Green, Eur.-Pat. 0150962, 17th Jan. 1985 (*CA:* **1986**, *104*, 129505p).
[12] T. Ishikawa, Y. Ohsumi, T. Kawai, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 819.
[13] D. Seebach, A. Thaler, A.K. Beck, *Helv. Chim. Acta* **1989**, *72*, 857.
[14] A. Thaler, D. Seebach, F. Cardinaux, *Helv. Chim. Acta* **1991**, *74*, 617, 628.
[15] D. Blaser, D. Seebach, *Liebigs Ann. Chem.* **1991**, in preparation.
[16] R. Imwinkelried, M. Schiess, D. Seebach, *Org. Synth.* **1987**, *65*, 230.
[17] D. Seebach, H. Bossler, H. Gründler, S. Shoda, R. Wenger, *Helv. Chim. Acta* **1991**, *74*, 197.
[18] H. Frank, G.J. Nicholson, E. Bayer, *J. Chromat. Sci.* **1977**, *15*, 174; W.A. König, 'The Practice of Enantiomer Separation by Capillary Gas Chromatography', Dr. A. Hüthig Verlag, Heidelberg, 1987, p. 25.
[19] M. Tominaga, M.T. Machini-Miranda, in 'Peptide Chemistry 1987, Proceedings of the Japan Symposium on Peptide Chemistry', Eds. T. Shiba and S. Sakakibara, Protein Research Foundation, Osaka, 1988, p. 227.
[20] M. Bodanszky, J.T. Sheehan, *Chem. Ind.* **1966**, 1597.
[21] H.C. Beyerman, H. Hindriks, E.W.B. de Leer, *J. Chem. Soc., Chem. Commun.* **1968**, 1688; E.M.S. Salem, *Pol. J. Chem.* **1979**, *53*, 1341; G.L. Reddy, E. Bikshapathy, R. Nagaraj, *Tetrahedron Lett.* **1985**, *26*, 4257.
[22] B. Halpern, L. Chew, V. Close, W. Patton, *Tetrahedron Lett.* **1968**, 5163.
[23] M.A. Barton, R.U. Lemieux, J.Y. Savoie, *J. Am. Chem. Soc.* **1973**, *95*, 4501; E.M. Salem, in 'Peptides; Structure and Biological Function, Proceedings of the Sixth American Peptide Symposium', Eds. E. Gross and J. Meienhofer, Pierce Chemical Company, Rockford, 1979, p. 507.
[24] G. Moore, D. McMaster, in 'Peptides, Proceedings of the Fifth American Peptide Symposium', Eds. M. Goodman and J. Meienhofer, J. Wiley and Sons, New York, 1977, p. 518; G. Moore, D. McMaster, *Int. J. Pept. Prot. Res.* **1978**, *11*, 140; G.J. Moore, Y.C. Kwok, *Can. J. Biochem.* **1980**, *58*, 641.
[25] B. Neises, T. Andries, W. Steglich, *J. Chem. Soc., Chem. Commun.* **1982**, 1132.
[26] D. Hudson, G.W. Kenner, *Int. J. Biol. Macromol.* **1980**, *2*, 63.
[27] M. Ueki, K. Kai, H. Horino, H. Oyamada, in 'Peptides 1988; Proceedings of the 20th European Peptide Symposium', Eds. G. Jung and E. Bayer, Walter de Gruyter & Co., Berlin, 1989, p. 145.
[28] Ch. Birr, in 'Reactivity and Structure Concepts in Organic Chemistry', Eds. K. Hafner, J.-M. Lehn, Ch.W. Rees, P. v. R. Schleyer, B.M. Trost, and R. Zahradnik, Springer-Verlag, Berlin, 1978, Vol. 8, p. 62; G. Barany, R.B. Merrifield, in 'The Peptides; Analysis, Synthesis, Biology', Eds. E. Gross and J. Meienhofer, Academic Press, New York, 1980, Vol. 2, Chapt. 1, p. 69; E. Atherton, R.C. Sheppard, 'Solid Phase Peptide Synthesis; a Practical Approach', IRL Press, Oxford, 1989, Chapt. 11, p. 149.
[29] A.R. Mitchell, B.W. Erickson, M.N. Ryabtsev, R.S. Hodges, R.B. Merrifield, *J. Am. Chem. Soc.* **1976**, *98*, 7357.
[30] IUPAC/IUB, *Pure Appl. Chem.* **1984**, *56*, 595.