19. *C*-Alkylation of Peptides through Polylithiated and LiCl-Solvated Derivatives Containing Sarcosine Li-Enolate Units

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(3.X.90)

The tripeptide and hexapeptide derivatives Boc-Gly-Sar-MeLeu-OH (**5b**), Boc-Ala-Sar-Sar-OH (**6b**), Boc-Ala-Sar-MeLeu-OH (**7b**), and Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OH (**12b**) can be poly-deprotonated (tri- and pentalithio derivatives **K** and **P**, respectively), and thus *C*-alkylated on sarcosine (Sar) moieties with MeI and allyl or $PhCH_2Br$. The polylithiated species are solubilized in THF, and their reactivity modified by excess base (lithium diisopropylamide (LDA)), by added LiCl, and/or the cosolvent *N,N'*-dimethylpropyleneurea (DMPU). Optimization of the reaction conditions for methylation in the cases of **7b** (*Table 3*) and **12b** (*Scheme 8*) gave products in which the Sar residue of the educt has been transformed into a Me-D-Ala unit in yields of 80 (**9c**/**8c**) and 67% (**14c**/**13c**), respectively, and with a diastereoselectivity of *ca.* 4:1. Less selective methylations and benzylations were observed with the tripeptides **5b** and **6b** containing only one stereogenic center; also, excess base and alkyl halide may lead to double alkylations in those latter two cases (*Tables 1* and *2*). No epimerization of stereogenic centers was detected under the strong-base conditions. The analysis of the products was accomplished by a combination of NMR and FAB-MS spectroscopy, as well as by hydrolysis to the parent amino acids, subsequent formation of derivatives with isopropyl isocyanate, and GC analysis on the chiral column *Chirasil-Val®*.

A) Introduction and Definition of the Goal. – Modified natural peptides and proteins are widely used for investigations of structure-activity correlations. For the synthesis of modified oligopeptides, the required amino acids are coupled in solution [1] [2] or by the *Merrifield* solid-phase technique [3–5]. Non-proteinogenic and unnatural amino acids with (*R*)- instead of (*S*)-configuration, with side chains not occurring in nature, or with additional substituents at N(α) or C(α) (α-branching) can, thus, be incorporated (see *a*) in *Scheme 1*). This procedure also allows to build into peptide chains more dramatically altered moieties[4]). Active-site and other modifications of proteins, enzymes, and antibod-

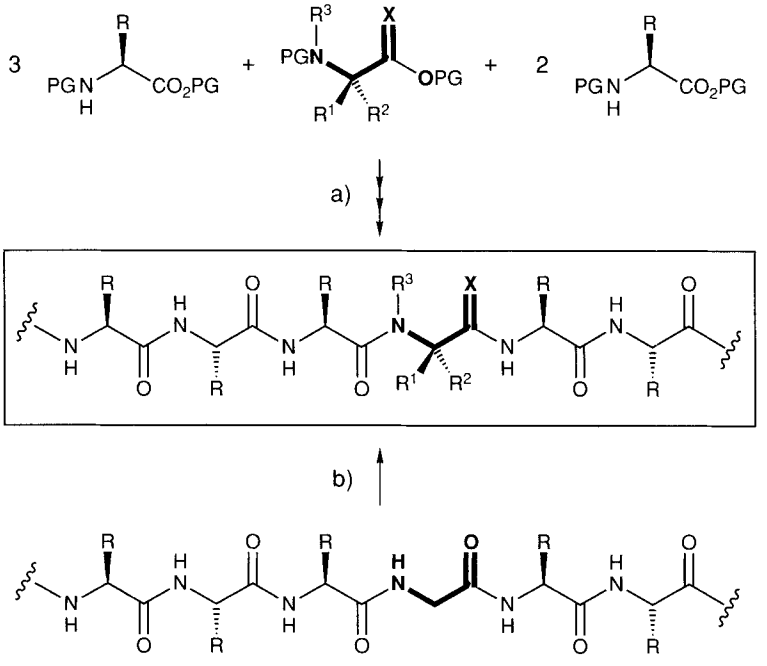
[1]) Part of the diploma thesis (ETH Zürich, 1989) and of the projected Ph. D. thesis of *H. B.*

[2]) Part of the Ph. D. thesis of *H. G.* (Dissertation No. 9171, ETH Zürich, 1990). A stipend from the *Stipendienfonds der Basler Chemischen Industrie zur Unterstützung von Doktoranden auf dem Gebiete der Chemie und der Biotechnologie* and financial support by the *Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung* (project No. 2.093-0.86 and project No. 20-25276.88) are gratefully acknowledged.

[3]) Postdoctoral fellow at ETH, 1984–1986. The stay of *S. S.* was financed by the *Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung* (project No. 2.093-0.86).

[4]) For instance β-amino acids, amino thioacids, (→endothiopeptides), ethylenediamines (→reduced peptides), 5-amino-4-oxo-amino acids (→oxomethylene peptides), α-hydroxy acids (→depsipeptides), phospho-amino or -hydroxy acids (→phosphopeptides, phosphono-depsipeptides). Other modifications are called thiomethylene-, hydroxymethylene-, carboretro- or inverso-, and alkene-peptides. For a review about such modifications, see [6].

Scheme 1. *Modification of Peptides* a) *by Assembly from Modified Amino Acids and* b) *by Reactions of a Glycine Moiety*. PG = protecting group.



ies are achieved by using nature's reagents [7], and was – until very recently [7c, d] – restricted to the 20 proteinogenic amino acids coded for in the DNA.

For the preparation of a series of peptides containing modifications at a specific site, it would be most attractive to be able to introduce new substituents by selective alkylation (see *b*) in *Scheme 1*). This would allow the chemist to synthesize larger amounts of an oligopeptide containing, *e.g.*, a glycine which is then *N*- or *C*-alkylated, or thionated[5]) to give a multitude of derivatives, without having to repeat the actual peptide synthesis with incorporation of various amino acids. Such a procedure might even provide derivatives which could not possibly be made from the components, because the corresponding amino acids would not be stable, *e.g.* α-hetero-substituted ones (R^1, R^2 = R_2N, R_2P, RO, RS, RSe; see *Scheme 1*)[6]).

Being 'carbanion chemists', we decided to activate glycine units for alkylations by deprotonation, *i.e.* enolate formation with strong base[7])[8]). At first sight, this idea of modifying peptides by reactions with electrophiles on a C-atom of the backbone looks neither realistic nor realizable. Due to the higher acidity of all NH protons along the chain, a poly-NH-deprotonated species would have to be generated prior to CH deproto-

[5]) We will report about the selective preparation of certain endothiopeptides from the parent oligopeptides in a separate paper.

[6]) For a publication about an α-amino-α-thio-carboxylic acid, see [8].

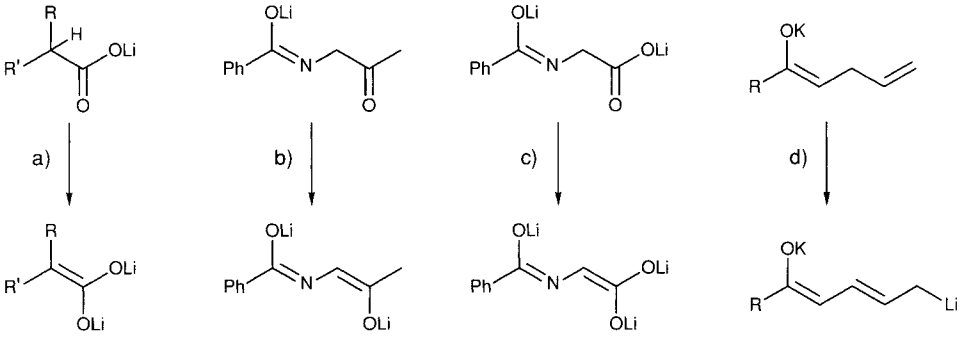
[7]) For attempts to modify peptides by photochemical rections, see *e.g.* the work by *Eilad* and coworkers [9].

[8]) In another project, we have investigated the possibility of modifying peptides by electrochemical conversions [10].

nation. This would require strong base in an aprotic solvent, conditions which are expected to lead to epimerizations of the stereogenic centers and to cause severe solubility problems. Our experience and knowledge about the structure and reactivity of Li compounds [11] [12] let us take a second sight at the problem, and serendipity was on our side.

B) Complications and How They Might Be Avoided. – Let us first turn to the problem of avoiding epimerization of (C=O)-substituted stereogenic centers. Although it is known that carboxylates [13], iminocarboxylates [14], and enolates [15] [16] may be further deprotonated (see *a*)–*d*) in *Scheme 2*), drastic conditions are required to do so; BuLi is

Scheme 2. *Polylithiated Carbonyl Derivatives Obtained by Multiple Deprotonation.* The configuration around double bonds and other structural features of these species are unknown and are not meant to be implied by the formulae used herein.



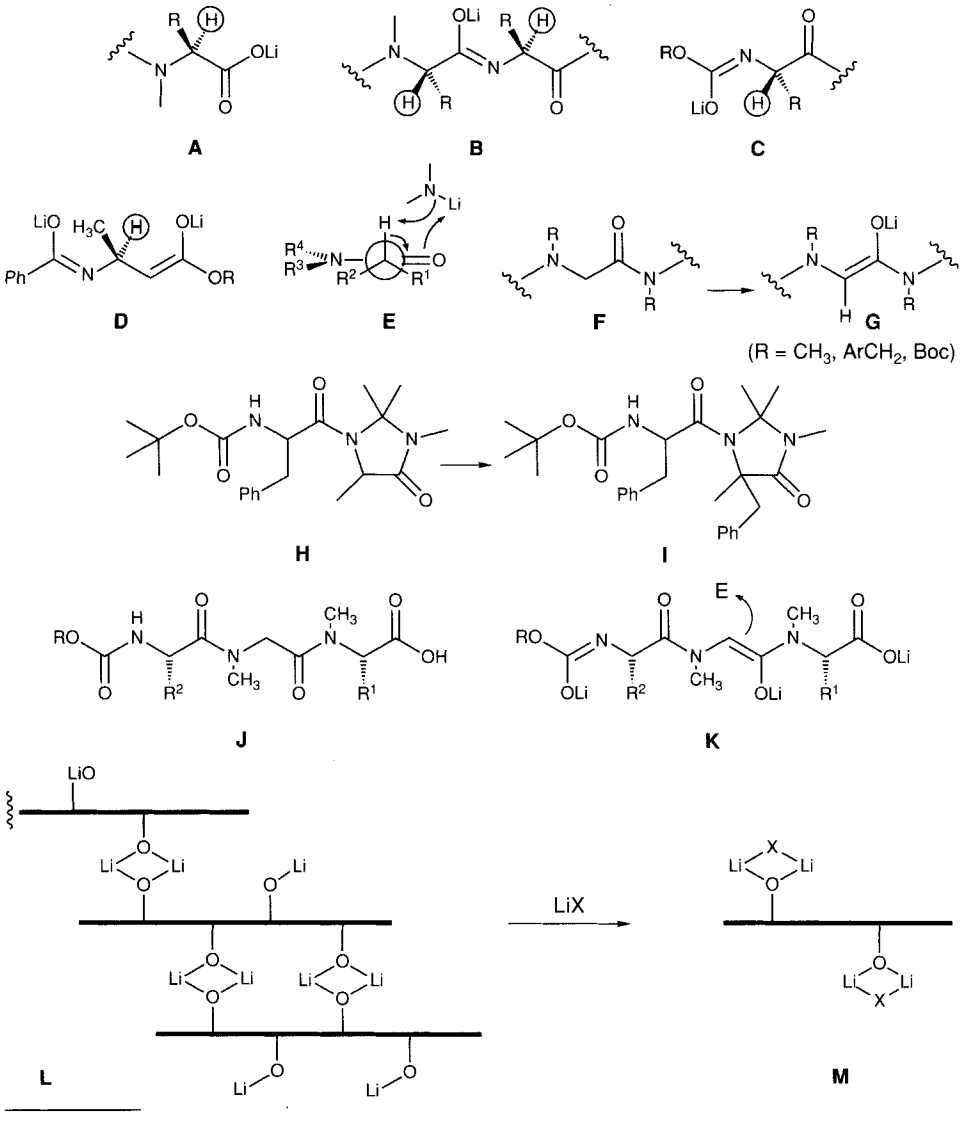
used to generate dilithiated carboxylic acids *a*) or ketone dianion derivatives *d*), and *C*-alkylation of *N*-benzoyl-glycine ('hippuric acid') takes excess lithium diisopropylamide (LDA)/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), but does not lead to double-alkylations *c*). Thus, it was to be expected that chirality centers next to a lithiated C-terminus (carboxylate **A**; *Scheme 3*), a lithiated internal amide linkage (azaenolate **B**), and a lithiated protected N-terminus (iminocarbonate *C*) of a peptide would be subject to a kind of protection; see also the configurationally stable dilithio derivative **D** of a β-amino acid [17].

Another problem is the need for selectivity of deprotonation at the desired amino-acid residue. Fortunately, there is another effect which could be exploited to favor enolate formation at a glycine moiety rather than at all other amino-acid residues: indeed deprotonation of α-branched amides is severely hampered by repulsion between a substituent at the N-atom and one at C(α) (R^2 and R^3 in **E** of *Scheme 3*)[9])[10]). This leads to the expectation that glycine residues with substituents at both N-atoms, should be deproto-

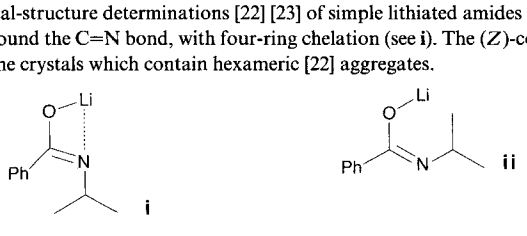
[9]) In the case of *Evans'* chiral *N*-acyl-oxazolidinones, this steric hindrance is believed to prevent formation of enolates from α-branched carboxylic-acid derivatives [18].

[10]) For generation of Li enolates from *N*,*N*-dialkylcarboxamides, see [19]. Crystal-structure determinations of such Li-enolates [11e] [20] show that the former amide N-atom which has become an enamine N-atom is strongly pyramidalized; the same effect is found in the structures of two silyl enol ethers derived from 1-acyl-3-methylimidazolidin-4-ones [21].

Scheme 3. *Lithiated Subunits of Peptides and Simple Lithiated Amides.* Here and in all other schemes, imines with (*Z*)-configuration and with the Li coordinated to an O-atom are drawn arbitrarily[11]).



[11]) It must be emphasized that the configurations around C=N and C=C bonds are drawn arbitrarily in all schemes; recent crystal-structure determinations [22] [23] of simple lithiated amides show a preference for the (*E*)-configuration around the C=N bond, with four-ring chelation (see **i**). The (*Z*)-configuration **ii** appears to be less favorable in the crystals which contain hexameric [22] aggregates.



nated faster (**F** → **G**) than the corresponding residues derived from higher amino acids[11]).

Yet another solution to the problem of achieving selective reactions at certain amino-acid residues within peptides would be to use the known [24] [25] N,N-acetals, such as **H**. This Boc-Phe-Ala-NHMe derivative could indeed be benzylated to give **I** (70% yield, 75% ds)[12]), but difficulties in preparing compounds of type **H** let us drop this approach.

Thus, we decided to use small peptides such as **J** containing a sarcosine (Sar) residue attached to another *N*-methylamino acid, hoping that we would be able to generate polylithiated species such as **K** for reactions with electrophiles[13]). Problems with limited solubility of these derivatives were overcome by the discovery that excess lithium diisopropylamide (LDA), the base used for the deprotonations, had a dramatic solubilizing effect[14]). The same effect could be produced by the addition of simple lithium salts such as LiCl. The origin of this solubilization is interpreted as being both, a common salt effect and a deaggregation of cross-linked aggregates between the polylithiated species to form mixed aggregates with the added salt (see **L** → **M** in *Scheme 3*). There is ample evidence for the existence of mixed aggregates in solution [11b] [28] and in the crystalline state, as well as for their involvement in reactions [12].

C) Starting Materials. Synthesis of Three Sar-Containing Tripeptides, and a Sar-Containing Hexapeptide. – The peptide derivatives **5b**, **6b**, **7b**, and **12** with which we carried out deprotonations and subsequent alkylations are shown in *Schemes 4* and *5*. They all contain a sarcosine/*N*-methylamino-acid subunit, a Boc-protected N-terminus, and a free carboxylic group at the C-terminus. Tripeptides **5b** and **6b** contain only one chiral amino acid, whereas tripeptide **7b** and hexapeptide **12** have a Sar residue flanked by two chiral amino-acid residues.

While the synthesis of **12**, a fragment of cyclosporin A (residues 2–7), and of its alkylated analogues **13** and **14** has been described previously [2] [29], the three Boc-tripeptides **5–7** had to be prepared in sufficient quantities (5–20 g at a time each) for the planned alkylation experiments.

The first steps were the couplings by conventional [30] activation with ethyl chloroformate of Boc-Gly-OH and Boc-Ala-OH with sarcosine benzyl ester toluene-4-sulfonate using Et_3N in toluene/$CHCl_3$ to give the Boc-protected dipeptide esters **1a** (80%) and **2a**

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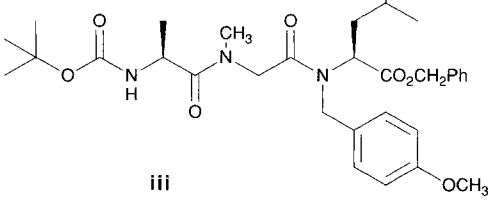
[12]) Hitherto unpublished experiments by *S. Shoda*[3]), ETH Zürich, 1985. Compare also the alkylations of dipeptide pivalaldehyde acetals [26].

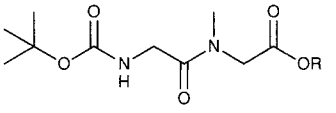
[13]) We also prepared a 4-methoxybenzyl derivative **iii** which could be debenzylated with $Ce(NH_4)_2(NO_3)_6$[2]). However, we encountered severe problems with the peptide coupling involving *N*-(4-methoxybenzyl)amino-acid derivatives, so that we did not further investigate this route (see also comment in *Footnote 15* below). 'Perbocylation' according to *Ragnarsson* and coworkers [27], and subsequent enolate formation with tripeptides is another avenue which we are currently probing; imidazolidinediones (cyclic ureas) are readily formed from these derivatives upon treatment with base[1]).



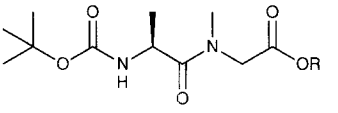
iii

[14]) First observed in our group by *C. W. Murtiashaw* (1984) in experiments with cyclosphorin A, hitherto unpublished experiments; mentioned in a review article [12b].

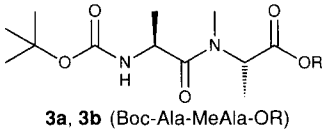
Scheme 4. *Tripeptides Used for the Alkylation Studies* (in boxes) *or Synthesized for Comparison to Identify the Expected Products.* The intermediate dipeptides are also shown. In all formulae **a** stands for the benzyl ester, **b** for the free acid, and **c** for the methyl ester (see workup of alkylation reactions, *Scheme 7, Sect. D*).



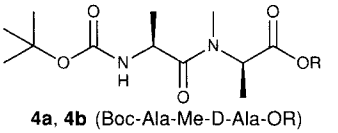
1a, **1b** (Boc-Gly-Sar-OR)



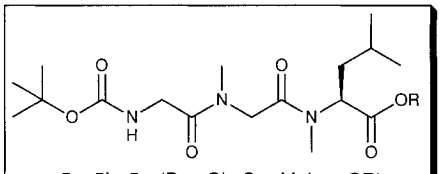
2a, **2b** (Boc-Ala-Sar-OR)



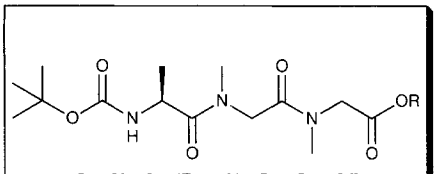
3a, **3b** (Boc-Ala-MeAla-OR)



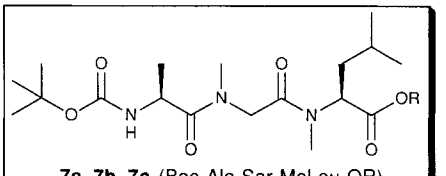
4a, **4b** (Boc-Ala-Me-D-Ala-OR)



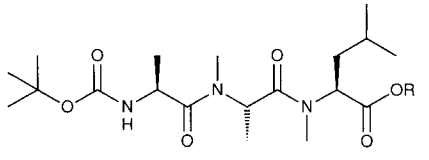
5a, **5b**, **5c** (Boc-Gly-Sar-MeLeu-OR)



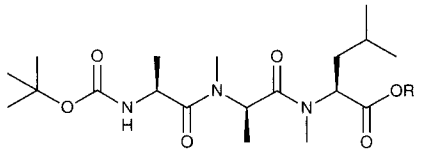
6a, **6b**, **6c** (Boc-Ala-Sar-Sar-OR)



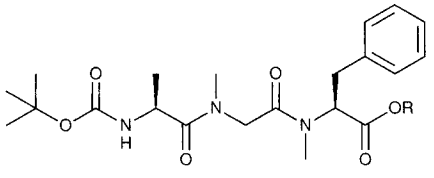
7a, **7b**, **7c** (Boc-Ala-Sar-MeLeu-OR)



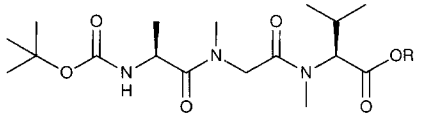
8a, **8b**, **8c** (Boc-Ala-MeAla-MeLeu-OR)



9a, **9b**, **9c** (Boc-Ala-Me-D-Ala-MeLeu-OR)



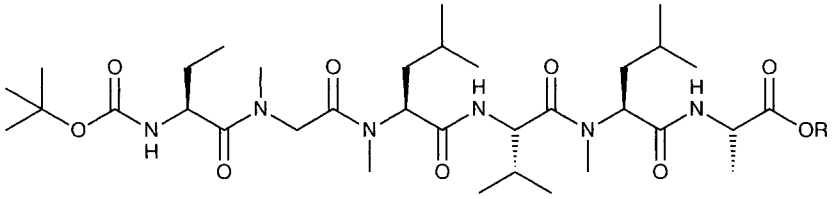
10a, **10b**, **10c** (Boc-Ala-Sar-MePhe-OR)



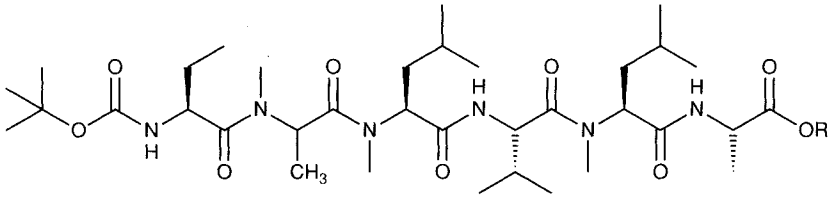
11a, **11b**, **11c** (Boc-Ala-Sar-MeVal-OR)

a R = $CH_2C_6H_5$ **b** R = H **c** R = CH_3

Scheme 5. *Boc-Protected* (**b**) *Hexapeptides and the Corresponding Methyl Esters* (**c**)



12b, **12c** (Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OR)



13b, **13c** (Boc-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OR)
14b, **14c** (Boc-Abu-Me-D-Ala-MeLeu-Val-MeLeu-Ala-OR)

(77%), respectively. Hydrogenative debenzylation (Pd/C in EtOH) led to the acids **1b** and **2b**. The subsequent coupling steps were carried out following procedures developed by *Wenger* [2] [29] and *Rich* and coworkers [31] for incorporation of *N*-methylamino acids into peptide chains[15]). Both demand careful control of the reaction conditions. We found that the mixed-anhydride activation with *t*-BuCOCl, requiring lower temperatures and longer reaction times, was more difficult to carry out than the procedure employing BOP-Cl[16]). Thus, coupling of the Boc-dipeptide **2b** with MeLeu-OCH_2Ph using *t*-BuCOCl took 60 h at −20° to yield after workup, chromatography, and recrystallization, 70% of the tripeptide derivative **7a**. On the other hand, activation of **2b** with BOP-Cl and coupling with ester could be done overnight at temperatures between 0 and 20°, yielding **7a** (90%) after the same purification steps[17]). Similarly, **5a** and **6a** were prepared from **1b** and **2b**, respectively.

The Boc-dipeptides **3** and **4** and Boc-tripeptide **8**–**11** were prepared for comparison purposes by one of the two coupling methods mentioned. Debenzylation of the intermediate esters **a** with H_2/Pd–C at room temperature and normal pressure gave the corresponding free acids **b** in essentially quantitative yields. All new compounds are fully described in the *Exper. Part.*

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[15]) Coupling with *N*-methylamino acids are known to be especially difficult due to an increased rate of epimerization ('racemization') [32].

[16]) BOP-Cl (= bis[2-oxooxazolidin-3-yl] phosphinic chloride) was introduced by *Diago-Meseguer et al.* [33].

[17]) With large-size runs, it turned out that it was advantageous to first let the BOP-Cl and the acid component react to completion before adding the amine component, rather than mixing all components and adding the coupling reagent BOP-Cl last, as recommended [31].

D) Analysis of the Peptides. – To detect whether diastereoisomeric mixtures had been formed during peptide coupling steps or by strong-base treatment, and to determine the structure of alkylation products, it was necessary to have an analytical tool other than NMR spectroscopy: oligopeptides, particularly *N*-methylated ones in organic solvents, tend to occur as mixtures of rotamers around the amide bond(s) which interconvert slowly on the NMR time scale so that spectra of shocking complexity may result. At higher temperatures (typically $\geqslant 120°$), rotation becomes fast, signals collaps, but the shift differences between protons of diastereoisomeric species are often too small for an unequivocal assignment. ^{13}C-NMR spectroscopy, on the other hand, is difficult to use for the determination of diastereoisomer ratios, especially if no reference samples are available (only for the methylation products of **7** and **12**, reference samples **8**/**9** and **13**/**14**, respectively, were available, see *Exper. Part*).

We, therefore, decided to analyze our peptides by hydrolysis to the D- and L-amino-acid, as well as D- and L-*N*-methylamino-acid components; ratios of diastereoisomeric peptides would, thus, be determined as ratios of enantiomeric amino acids. We tested most of the available methods for the analytical separation of enantiomeric amino acids: formation of derivatives with chiral auxiliaries and chromatographic separation of the resulting diastereoisomers ('chiral Fmoc' [34])[18]), use of a chiral mobile phase[19]) on a reversed-phase HPLC column [35], ligand-exchange chromatography with Cu(II) in the mobile phase and a stationary phase containing covalently bound proline[20]) [36–39], TLC with a similar chiral stationary phase [40][21]), and GC [42] of suitable derivatives on various chiral phases. Using the thermally stable *Chirasil-Val*® GC column [43] and amino-acid derivatives obtained with isopropyl isocyanate [44] (*Scheme 6*)[22]) turned out to be most suitable for the type of amino acids occurring in our peptides[23]): except for the two mixtures *N*-methyl-D/L-phenylalanine and D-alanine/*N*-methyl-D-alanine[24]), all other components gave rise to base-line separated GC peaks. To test the reliability of the method, which is supposed to be free of racemization [44], we subjected the tripeptide mixture Boc-Ala-MeAla-MeLeu-OMe/Boc-Ala-Me-D-Ala-MeLeu-OMe (**8c**/**9c**) and the hexapeptide mixture Boc-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OMe/Boc-Abu-Me-D-Ala-MeLeu-Val-MeLeu-Ala-OMe (**13c**/**14c**) to hydrolysis and the resulting mixtures of amino acids to Me_2CHNCO treatment as indicated in *Scheme 6*. GC analysis of the

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[18]) Slow rates of formation for derivatives of *N*-methylamino acids and lacking separation of *N*-methylalanine from sarcosine were observed with this method.

[19]) Using phenylalanine/Cu(II) in the mobile phase, we were unable to cleanly separate alanine and *N*-methylalanine by this method.

[20]) We encountered problems with the reproducibility [39] of the LEC method [36], which separates normal and *N*-methylamino-acid enantiomers quite well, but not mixtures of several different amino acids.

[21]) While single amino-acid enantiomers separate well on the commercially available (*Macherey-Nagel*) chiral TLC plates of this type, mixtures were difficult to analyze. Thus, a mixture of sarcosine, *rac*-alanine, *rac*-*N*-methylalanine, and *rac*-*N*-methylleucine did not give seven well separated spots under the usual conditions. Furthermore, quantitative analysis of TLC spots is difficult to do without special equipment, especially since *N*-methylamino acids give a *much* weaker ninhydrin coloration than normal amino acids [41].

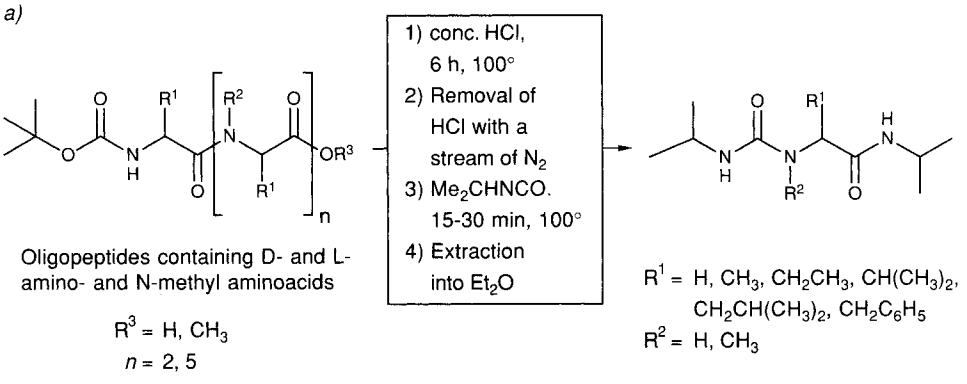
[22]) Derivatives obtained with perfluoroanhydrides were shown not to be suitable for *N*-methylamino acids [45].

[23]) A modified column ('*XE-60*-L-valin-(*S*)-α-phenylethylamid') was recommended [46] for the separation of *N*-methylamino-acid derivatives; we used the more readily available (see *Exper. Part*) *Chirasil-Val*® column with – almost – no problems (see text).

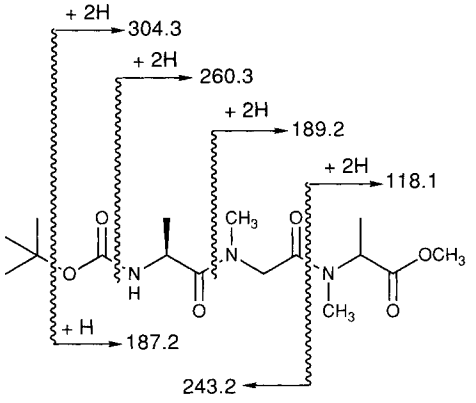
[24]) Thus, the ratios given for those pairs of amino acids are not as accurate as those for the other components.

Scheme 6. *Analysis of the Peptides. Using* a) *Hydrolysis and Formation of Derivatives for GC Analysis on a Chiral Column (Chirasil-Val®) [43] [44] and* b) *Sequencing by FAB-MS*

a)



b)



Methylation product of **6b**

derivatives gave the same ratios of diastereoisomers **8a**/**9b** and **13**/**14** as those independently determined by ^{13}C-NMR of these tripeptide and hexapeptide mixtures and comparison with authentic samples[25][26]). This test also confirmed that no racemization of the amino acids had occurred within detection limits of the method (if carried out correctly[26]). We routinely determined the purity of all synthesized peptide derivatives by this method to make sure that no racemization of amino acids had taken place under the coupling conditions.

Another important method for the analysis of our Boc-peptide alkylation products was mass spectroscopy [47]. We noticed that in the FAB-MS (fast-atom-bombardment MS; 3-nitrobenzyl-alcohol matrix), the loss of the Boc group gives rise to a major peak.

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[25]) The peptides **8** and **9** were synthesized for comparison by coupling as described in the *Exper. Part.* Mixtures of them could not be separated by chromatography. Mixtures of **13c** and **14c** could be separated by flash chromatography, and the pure samples were compared with authentic samples [2].

[26]) We noticed that MeLeu-OH may partially racemize. We have indications that this happens on treatment with excess isopropyl isocyanate, if there is free MeLeu-OH present, rather than its hydrochloride. It is recommended to perform at least two parallel runs, especially with MeLeu-OH-containing samples.

The resulting ion fragments further, with the CO–N bonds breaking so that the sequence of the peptide, starting from the N-terminus, can be read from the FAB-MS mass spectrum (*Scheme 6, b*). In the case of the tripeptide **6b** containing two sarcosine moieties, the MS method was the easiest way to determine the site of alkylation. With the other alkylated Boc-peptides, the structures determined by NMR spectroscopy and by the above described GC method were confirmed by the FAB-MS.

E) Poly-lithiations of the Boc-Peptides 5b, 6b, 7b, and 12b and Reactions with Electrophiles. – The general reaction conditions for alkylations of Boc-protected tripeptides are given in *Scheme 7*, and the specific applications to Boc-Gly-Sar-MeLeu-OH (**5b**), Boc-Ala-Sar-Sar-OH (**6b**), and Boc-Ala-Sar-MeLeu-OH (**7b**) yielding products **7c–9c** and **15–22**, **10c** and **23–30**, and **8c/9c** and **31–43**, respectively, are collected in *Tables 1–3*, respectively. The conditions were originally optimized with **7b** (*Table 3*) and the hexapeptide **12b** (see below). Methylations with **7b** showed that the yield could be increased by the addition of LiCl (*Table 3, Entries 1–5*) which renders the reaction mixture homogeneous and better stirrable (see the discussion in *Chapt. B*). The increased yield upon addition of BuLi *after* deprotonation with LDA can be explained as follows: it was noticed earlier that complexes **N** of Li-enolate aggregates with $(i\text{-Pr})_2NH$ may be present in LDA-generated Li-enolate solutions in which the amine forms a H-bridge with the enolate moiety; this 'secondary-amine' effect was made responsible for 'reprotonations' and formation of starting material upon addition of electrophiles [11e] [12b] [26]. Thus, the removal of $(i\text{-Pr})_2NH$ by addition of BuLi may cause an increase in the yield,

Scheme 7. *Conditions for Alkylations of Boc-tripeptides.* Samples of crude Boc-peptides or of the isolated chromatographed mixtures of epimeric Boc-tripeptide methyl esters were analyzed by hydrolysis to the amino acids, formation of derivatives, and GC analysis (see *Scheme 6*).

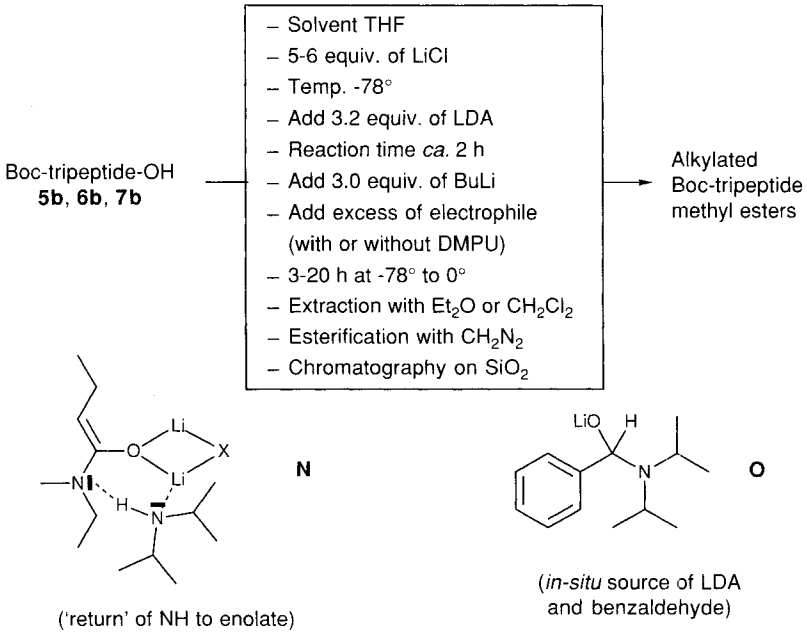
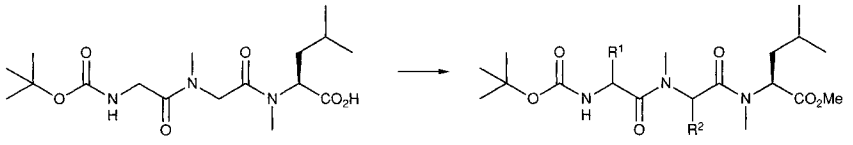


Table 1. *Products from the Methylation and Benzylation of the Boc-tripeptide* **5b.** If not stated otherwise, conditions as specified in *Scheme 7.*



5b (Boc-Gly-Sar-MeLeu-OH)

Electrophiles, conditions	Products	R^1	R^2	Yield [%]	Ratio (D/L)
7.2 equiv. of MeI	**5c** (from educt)	H	H	8	–
3.5 h, −18°	**15/16**	H	Me	62	2:1
(10% DMPU)	**17/7c**	Me	H	4	1:1
	8c/9c/18	Me	Me	22	–[a])
6.7 equiv. of $PhCH_2Br$,	**5c** (from educt)	H	H	25	–
6 h, −18°, 0.5 h, 0°	**19/20**	H	$PhCH_2$	6	1:1
(10% DMPU)	**21/22**	$PhCH_2$	H	31	1:1

[a]) All four possible isomers are formed: **8c** and **9c** were identified by comparison with authentic material (see also methylation of **7b**). The other two isomers (**18**) must be Boc-D-Ala-MeAla-MeLeu-OR and Boc-D-Ala-Me-D-Ala-MeLeu-OR. The ratio (Me-D-Ala + D-Ala)/(Me-L-Ala + L-Ala) in the product mixture is 1.5:1 (determined by hydrolysis and GC analysis).

Table 2. *Products from the Methylation and Benzylation of the Boc-tripeptide* **6b.** If not stated otherwise, conditions as specified in *Scheme 7.* The material balance was especially poor in this case, because **6b** and – to a lesser extent the produced acids – are rather well soluble in H_2O and were not totally extracted into the organic phase during workup. The ratio of product peptides formed might be slightly changed during workup due to differential distribution between the aqueous and organic phase.

6b (Boc-Ala-Sar-Sar-OH)

Electrophiles, conditions	Products	R^1	R^2	Yield [%]	Ratio (D/L)
5 equiv. of MeI,	**6c** (from educt)	H	H	48	–
20 h, −78°	**23/24**	Me	H	9	1:1
(no BuLi, no DMPU added)					
5 equiv. of MeI,	**6c** (from educt)	H	H	12	–
17 h, −26°	**23/24**	Me	H	33	1:1
(no BuLi, with 10% DMPU)					
7.2 equiv. of MeI,	**6c** (from educt)	H	H	23	–
20 h, −78°	**23/24**	Me	H	9	1.3:1
(no DMPU added)	**25/26**	H	Me	17	1:1
	27	Me	Me	17	[a])
7.0 equiv. of MeI,	**23/24**	Me	H	12	1:2.5
3 h, −18°	**25/26**	H	Me	5	1:1.2
(10% DMPU added)[b])	**27**	Me	Me	26	[a])

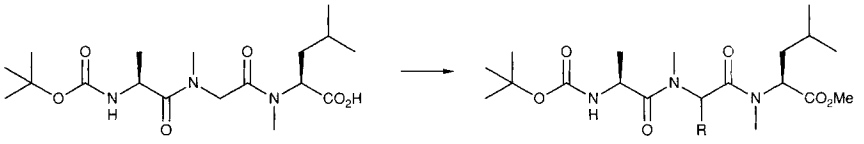
Table 2 (cont.)

Electrophiles, conditions	Products	R^1	R^2	Yield [%]	Ratio (D/L)
7.0 equiv. of $PhCH_2Br$,	**6c** (from educt)	H	H	14	–
22 h, –26°	**28/29**	$PhCH_2$	H	29	1:2
(10% DMPU added)	**30/10c**	H	$PhCH_2$	12	1:1

[a]) It is not possible to distinguish between the two MeAla units formed, by the analysis used herein. All four possible diastereoisomers were formed.

[b]) No starting material, *i.e.* **6c**, recovered.

Table 3. *Reactions of the Boc-tripeptide* **5b** *with Different Electrophiles.* All reactions were carried out at –78°, without allowing to warm before workup, for 12–20 h in the case of alkyl halides and for 1–3 h in the case of aldehydes as electrophiles. Six equiv. of electrophile per peptide were employed in all cases. Workup, esterification with CH_2N_2, and chromatography followed the procedure specified in *Scheme 7*. The methylation of **7b** was used for the optimization and elaboration of the general procedure given in *Scheme 7*. (All other reactions described in this paper were not optimized!)



7b (Boc-Ala-Sar-MeLeu-OH)

Electrophile	Products	R	Equiv. of LDA	LiCl	BuLi	Yield [%] (**7c**)	Ratio (D/L)
MeI	**9c/8c**	Me	2.3	–	–	< 5 (> 90)	–
			3.2	–	–	35	1.7:1
			3.2	–	3.2	42	
			3.2	5	–	50 (25)	3.2:1
			3.2	6	3.2	80 (8)	3.7:1
EtI[a])	**31**	Et	3.2	7	3.2	11 (48)	[b])
CH_2CHCH_2Br[a])	**32/33**	$R = CH_2{=}CHCH_2$	3.2	6	3.2	32 (48)	5:1
–[c])	**34/35**	Pr	–	–	–	–	5:1
$PhCH_2Br$[a])	**36/37**	$PhCH_2$	3.2	7	3.2	20	> 20:1
CH_3CHO	**38**	MeCH(OH)	3.2	6	3.2	40	1.5:1[d,e])
t-BuCHO	**39**	*t*-BuCH(OH)	3.2	6	3.2	42	–[e])
PhCHO	**40/41**	PhCH(OH)	3.2	5	3.2	72	2:1:1:1[e])[f])
	42/43						

[a]) 10–15% of DMPU added as a cosolvent, with the alkylating reagent.

[b]) Not determined.

[c]) By catalytic hydrogenation of **32/33.** The ratio of diastereoisomers was determined by hydrolysis to the amino acids and GC analysis (the enantiomeric 2-amino-*N*-methylpentanoic acids (= *N*-methylnorvaline) separated well on the *Chirasil-Val*® column).

[d]) Only two of the four possible diastereoisomers were detected (by the usual GC analysis).

[e]) No assignment of the configuration of the products formed.

[f]) Three of the four diastereoisomers could be separated by column chromatography. The ratio of diastereoisomers could be determined by ^1H- and ^{13}C-NMR spectroscopy.

although excess equivalents (3 in the present case) of strong Li-amide base are thus generated and will be in the solution together with the enolate and, notably, with the electrophile added, as well as with the product formed. Inspite of that, the yield of methylation of the Boc-tripeptide **7b** to give **8c** and **9c** rises from 50 to 80% (67 to 87%,

based on unaccounted **7b**) when BuLi is added before excess MeI (*Entries 4* and *5* in *Table 3*). Also, the selectivity increases by this measure, albeit to a lesser extent. Two other facets of this reaction are noteworthy: within the detection limits of the analytic method chosen, the two stereogenic centers of **7b** are not epimerized under these strongly basic conditions, and there is no *N*-methylation of the Boc-protected N-terminus in **7b** by the large excess of MeI and base. To obtain the products of allylation and benzylation, **32**/**33** and **36**/**37**, respectively, from the Boc-tripeptide **7b**, the aprotic dipolar cosolvent *N*,*N*′-dimethylpropyleneurea (DMPU) [48] had to be added together with the alkyl halides. The allyl substituent of **32**/**33** was catalytically hydrogenated to a propyl group (→**34**/**35**) before acidic peptide hydrolysis for the GC analysis. Aldehyde electrophiles (→ **38**–**43**) did, of course, not require a cosolvent to react. On the other hand, it is surprizing that the enolizable acetaldehyde gave a product at all when added to the LDA-containing solution of polylithiated **7b** (→ **38**). With benzaldehyde, the yield of adducts **40**–**43** is especially high, which may be due to the primary and temporary formation of the adduct **O** (*Scheme 7*), a known [49–51] 'slow-release' source of both LDA and benzaldehyde[27]).

As can be seen from *Tables 1* and *2*, the excess base generated by BuLi deprotonation of $(i\text{-Pr})_2NH$ formed in the polylithiation step indeed causes severe selectivity problems, when the tripeptides, such as **5b** (*Table 1*) or **6b** (*Table 2*) contain two possible CH_2-deprotonation sites. The regioselectivity and the stereoselectivity drop, and there are double alkylations with MeI (not with $PhCH_2Br$), as seen from the products obtained **5b** (**7c**–**9c**, **15**–**22**) and from **6b** (**10c**, **23**–**30**). When $(i\text{-Pr})_2NH$ is left in the mixture, as checked with Boc-Ala-Sar-Sar-OH (**6b**), the total yield of methylation product decreases, no matter, whether DMPU is added or not (*Entries 1* and *2* in *Table 2*). Interestingly, under these conditions, the product **25**/**26**, arising from monomethylation at the C-terminal amino acid can hardly be detected and the doubly methylated product **27** not be found at all. With BuLi added for removal of $(i\text{-Pr})_2NH$ (→LDA), the total yield of methylation products is remarkably higher (*Entries 3* and *4* in *Table 2*), but the amount of **25**/**26** increases, and **27** can also be found. The experiments with Boc-tripeptides containing glycine or sarcosine at the terminal positions show that doubly lithiated species (*cf. Scheme 2*) are formed and give rise to alkylation next to a deprotonation site. Although alkylation yields of up to 62% (67% based on recovered educt) can be obtained on BuLi treatment, the selectivities never exceed 2:1 with the tripeptide derivatives **5b** and **6b** containing two glycine (or sarcosine) units.

The Boc-hexapeptide **12b** [29] could be methylated under solubilization of the pentalithio derivative (**P** in *Scheme 8*) either with excess LDA or with LiCl. On BuLi treatment, a surprizingly high yield (67%) of only two methyl esters **13c** and **14c** (1:4) could be isolated, using a procedure similar to that given in *Scheme 7* above. The two diastereoisomers **13c** and **14c** were separated by chromatography and identified by comparison with authentic samples which had both been obtained in the course of syntheses of cy-

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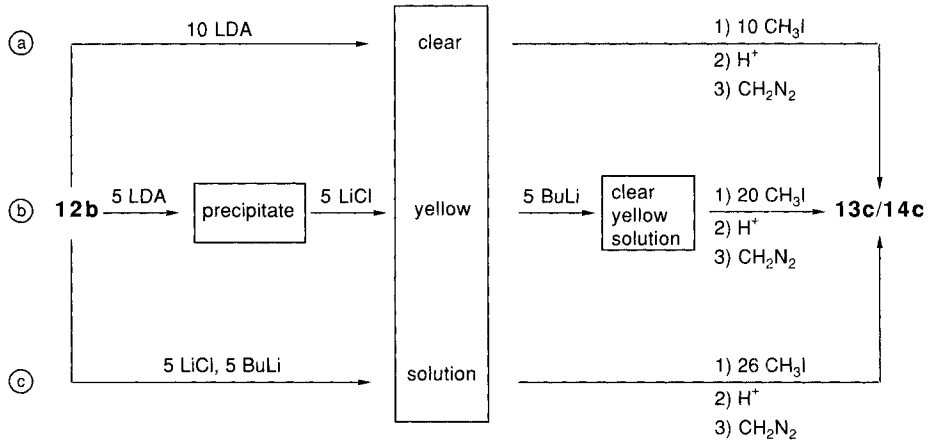
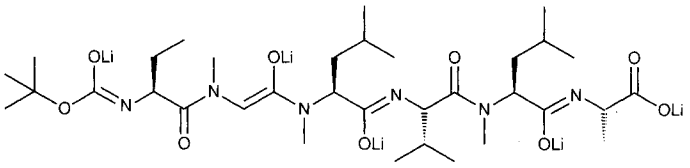
[27]) This effect was originally discovered in experiments directed towards the generation of unstable enolates from a β-RS-substituted carbonyl compound derived from cysteine [49]. It was shown that the adducts of *t*-BuOLi to aromatic aldehydes could also be used as bases and *in-situ* sources of the aldehydes for reactions of unstable enolates [50]. The effect was recently also observed in additions [51] of the unstable [52] nitronate from nitrocyclopropane to benzaldehyde.

Scheme 8. *Methylation of the Boc-hexapeptide* **12b** *to the Boc-hexapeptide* **14c** via *a Pentalithio Derivative* **P** *with a Diastereoselectivity of up to 80% ds.* Solubilization can be attained either by using twofold excess of LDA or by adding 5 equiv. of LiCl. Removal of $(i\text{-}Pr)_2NH$ by adding BuLi raises the yield and the stereoselectivity. The actual structure of **P** ((*E*/*Z*)-double bonds, Li on O or N, aggregation state, *etc.*) is unknown.



Yield and ratio of **13c**/**14c**: ⓐ 31% (1:2); ⓑ 67% (1:4); ⓒ 64% (1:4.3)

P



closporin-A analogues[28]) [2]. As mentioned in *Chapt. D*, the amino-acid composition of **13c** and **14c** was confirmed by degradation and GC analysis (*Scheme 6*). The missing material in the reaction producing 67% of **13c**/**14c** consisted of educt ester **12c** and compounds moving faster on chromatography. Although the polydeprotonated species **P** contains three 'azaenolate' units and five stereogenic centers, we did not detect by-products or impurities which contained more than the three *N*-methylamino acids already present in the starting material **12b**, or epimers of **12c**, **13c**, or **14c**, or peptides bearing Me groups at quaternary C-centers (α-branched amino acids).

G) Conclusions. – The experiments described here demonstrate that Boc-oligopeptides[29]) can be converted to polylithiated species, solutions of which can be stirred and handled for reactions with electrophiles if prepared in the presence of excess lithium salts (LiX). After removal of all more acidic protons (–CO_2H and –CONH–), CH_2 groups of glycine and sarcosine residues within these peptides are deprotonated with formation of enolates which are *C*-alkylated. The most selective reactions were observed in those

[28]) The syntheses of numerous cyclosporin-A analogues [2] was carried out following the same procedures as elaborated for cyclosporin A itself [29]. Some details are described in the patent literature [53].

[29]) Z-Protected oligopeptides have also been polylithiated; the $PhCH_2O$ group may, however, cause problems under the very strongly basic reaction contitions. For *C*-alkylation of Z-protected phosphono peptides *via* polylithiated derivates see *Ch. Gerber*, Ph. D. thesis ETH Zürich, 1991.

Scheme 9. *Structural Features of Selective C-Alkylations of Backbone CH_2 Groups in Oligopeptides*

Q **R**

cases (**7**, **12**), in which a sarcosine residue was attached to another *N*-methylamino acid and flanked by two 'normal' amino acids, bearing side chains (see **Q** → **R** in *Scheme 9*). It turns out that no more than traces of products arising from *N*-alkylation or from epimerization of the amino-acid moieties present in the educt peptide are formed under the conditions chosen by us. It appears, from the few cases studied so far, that the reaction works better with larger peptides containing aliphatic side chains. With (*S*)-configuration of the amino acids in the peptide, the newly-formed stereogenic center tends to have (*R*)-*configuration*.

Experimental Part

1. *General.* THF was freshly distilled from K under Ar. CH_2Cl_2 was distilled from P_2O_5. Abs. Et_2O was purchased from *Fluka* (*puriss.*), otherwise Et_2O was distilled from NaOH. BuLi was used as a 1.4N soln. in hexane. Boc-Abu-Sar-MeLeu-Val-MeLeu-Ala-OH (**12b**), Boc-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OH (**13b**), and Boc-Abu-Me-D-Ala-MeLeu-Val-MeLeu-Ala-OH (**14b**) were available from cyclosporin and cyclosporin-analogue syntheses [2] [29] [53] [55]. Unless otherwise stated, org. extracts were dried ($MgSO_4$) and evaporated using a rotary evaporator. TLC: *Merck* silica gel *60* F_{254} anal. plates; detection either with UV, or dipping in a soln. of 10 ml of anisaldeyde, 10 ml of conc. H_2SO_4, 5 ml of AcOH, and 275 ml of EtOH, or dipping on a soln. of 600 mg of ninhydrin, 2 ml of AcOH, 13 ml of H_2O, and 285 ml of BuOH, followed by heating. LC: at 0.3–0.5 atm, *Merck* silica gel *60* (230–400 mesh). GC: *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: *A*, 5 min 160°, 2°/min, 10 min 200°; *B*, 5 min 160°, 1°/min, 10 min 200°. M.p.: *Büchi-510* apparatus; uncorrected. Optical rotations: 10-cm, 1-ml cell, *Perkin-Elmer-241* polarimeter. IR spectra: *Perkin-Elmer-782* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$ at r.t. *Bruker-WM-300* (300 resp. 75 MHz), *Varian-Gem-200* (200 MHz), *Varian-EM-390* (90 MHz), or *Varian-FT-80A* (80 MHz) instrument; peptide numbering according to [54]. FAB-MS: *VG-ZAB2-SEQ* in a 3-nitrobenzyl alcohol matrix; in *m/z* (% of basis peak). Ape(4-en) = (*S*)-2-aminopent-4-enoic acid; Ser(3-Bu^t) = 3-*C*-(*tert*-butyl)serine, Ser(3-Ph) = 3-*C*-phenylserine.

2. *General Procedure for the Alkylation of Peptides.* Unless otherwise stated, the following procedure was used: To a soln. of $(i\text{-}Pr)_2NH$ (0.6 ml, 4.23 mmol) in THF (10 ml) under Ar, 1.43N BuLi in hexane (3.0 ml, 4.3 mmol) was added at 0°. After 20 min stirring at 0°, this soln. was cooled to −78°. Separately, a soln. of the desired peptide (1.3 mmol) and dry LiCl (8 mmol) in THF (20 ml) was prepared under Ar and cooled to −78°. The LDA soln. was transfered to the peptide soln. *via* a *Teflon* tube. After 2 h stirring, 1.43N BuLi (3.0 ml), DMPU where stated (*Tables 1–3*), and the appropriate electrophile were added in 10 min intervals. If not otherwise mentioned, the following workup procedure was used: After the addition of 1N H_2SO_4 at −78°, the mixture was extracted with Et_2O (100 ml). The org. layer was washed 2–3× with sat. NaCl soln. (to which some drops of 1N NH_3 had been added), until the H_2O layer reached a pH of 4. The combined org. layers were dried ($MgSO_4$) and evaporated. To the crude product in Et_2O (10 ml) diazomethane in Et_2O was added dropwise until persistence of the yellow color. The excess diazomethane was destroyed by adding some drops of AcOH. Washing with sat. $NaHCO_3$ and sat. NaCl soln., drying ($MgSO_4$), and evaporation gave the product which then was purified.

3. *General Procedure for GC Analysis.* In a screw-capped vial, 20–50 mg of peptide was hydrolyzed with conc. HCl soln. at 100–110° for 6–16 h. Then H_2O was removed in an airflow or a stream of N_2, distilled isopropyl isocyanate (100 µl) added, and the vial tightly closed. Heating at 100° for 10–15 min followed by removal of excess isocyanate in an airflow or a stream N_2 gave the derivatives of the individual amino acids. This crude product was extracted with Et_2O and the soln. evaporated to a suitable volume and injected onto the *Chirasil-Val®* column.

4. *Starting Materials. Boc-Gly-Sar-OCH$_2$Ph* (**1a**). A soln. of Boc-Gly-OH (9.76 g, 55.7 mmol) in toluene (55 ml), $CHCl_3$ (55 ml), and Et_3N (7.8 ml, 56 mmol) was cooled to −17°. Then ethyl chloroformate (6.7 ml, 6.9 mmol) was added dropwise. After stirring for 20 min, a soln. of sarcosine benzyl ester toluene-4-sulfonate (20.7 g, 59 mmol) and Et_3N (8.2 ml, 59 mmol) in $CHCl_3$ (110 ml) was added dropwise within 1 h. Then, the temp. was raised to r.t. and the mixture stirred at 50° for 30 min. The resulting soln. was washed with 1N HCl, sat. NaCl soln., 0.5M $KHCO_3$, and sat. NaCl soln., and each of the aq. solns. was extracted twice with CH_2Cl_2. The collected org. phases were dried ($MgSO_4$) and evaporated. Flash chromatography (FC; silica gel, hexane/AcOEt/acetone 10:10:1) gave 15.05 g (80%) of **1a**. TLC: R_f 0.36 (hexane/AcOEt/acetone 10:10:1, anisaldehyde). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.43 (*s*, *t*-Bu); 3.0 (*s*, CH_3–N(2.2)); 4.01 (*m*, 2 H–C(2.1)); 4.17 (*s*, 2 H–C(2.2)); 5.18 (*s*, PhCH_2); 7.33 (*s*, *Ph*CH$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.34 ((*C*H$_3$)$_3$C); 35.25 (CH_3–N(2.2)); 42.28 (CH_2(2.1)); 49.60 (CH_2(2.2)); 67.12 (PhCH_2); 79.68 ((CH$_3$)$_3$*C*); 128.35, 128.52, 128.66 (5CH, *Ph*CH$_2$); 135.20 (1C, *Ph*CH$_2$); 155.77 (*t*-BuO*C*O); 168.73 (C(1.1)); 169.31 (C(1.2)).

Boc-Gly-Sar-OH (**1b**). To a soln. of **1a** (15.0 g, 44.5 mmol) in EtOH (200 ml), 10% Pd/C (312 mg) was added. The flask was evacuated and filled with H_2 twice. After stirring at r.t. for 18 h, the soln. was filtered through *Celite* and evaporated, yielding **1b** (10.9 g, 99%). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*s*, *t*-Bu); 2.99, 3.03 (2*s*, CH_3–N(2.2) rotamers); 3.92–4.14 (*m*, 2 H–C(2.1), 2 H–C(2.2)); 5.70 (br. *m*, H–N(2.1)); 9.09 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.34 ((*C*H$_3$)$_3$C); 35.25, 35.44 (CH_3–N(2.2)); 42.20, 42.25 (CH_2(2.1)); 49.60, 50.26 (CH_2(2.2)); 80.06 ((CH$_3$)$_3$*C*); 156.14, 156.50 (*t*-BuO*C*O); 169.99, 172.05 (C(1.1), C(1.2)). FAB-MS: 269.4 (9, $[M+23]^+$, $C_{10}H_{18}N_2O_5Na^+$), 274.4 (13, $[M+1]^+$, $C_{10}H_{19}N_2O_5^+$), 191.3 (46, $C_6H_{11}N_2O_5^+$), 147.2 (70, $C_5H_{11}N_2O_3^+$), 89.6 (36, $C_3H_8NO_2^+$), 56.2 (100, $C_4H_8^+$).

Boc-Ala-Sar-OCH$_2$Ph (**2a**). As described for **1a**, with Boc-Ala-OH (12.9 g, 68 mmol), toluene (70 ml), $CHCl_3$ (70 ml), Et_3N (9.6 ml, 68 mmol) ethyl chloroformate (6.7 ml, 69 mmol; 30 min), sarcosine benzyl ester toluene-4-sulfonate (25.3 g, 72 mmol), Et_3N (10 ml, 72 mmol), and $CHCl_3$ (140 ml; within 2 h). FC (silica gel, hexane/AcOEt 2:1) gave 18.33 g (77%) of **2a**. TLC: R_f 0.35 (hexane/AcOEt 2:1, anisaldehyde). $[\alpha]_D^{r.t.} = -7.8$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.23, 1.30 (2*d*, $J = 7$, 7, CH_3(3.1) rotamers); 1.40, 1.42 (2*s*, *t*-Bu); 2.96, 3.10 (2*s*, CH_3–N(2.2), rotamers); 3.92, 4.39 (*AB*, $J = 17$, 2 H–C(2.2)); 4.6 (*m*, H–C(2.1)); 5.15, 5.18 (2*s*, PhCH_2); 5.44 (*d*, $J = 8$, H–N(2.1)); 7.34 (*s*, *Ph*CH$_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.81 (CH_3(3.1)); 28.39 (*C*H$_3$)$_3$C); 36.33 (CH_3–N(2.2)); 46.32 (CH(2.1)); 49.75 (CH_2(2.2)); 67.08 (PhCH_2); 79.60 ((CH$_3$)$_3$*C*); 128.38, 128.51, 128.67 (5CH, *Ph*CH$_2$); 135.31 (1C, *Ph*CH$_2$); 155.12 (*t*-BuO*C*O); 168.75 (C(1.1)); 173.60 (C(1.2)).

Boc-Ala-Sar-OH (**2b**). As described for **1b**, with **2a** (25.4 g, 72.5 mmol), EtOH (350 ml), and 10% Pd/C (480 mg; 14 h): 18.7 g (99%) of **2b**. $[\alpha]_D^{r.t.} = -5.9$ ($c = 0.95$, $CHCl_3$). IR: 3410, 2980, 2940, 1710, 1655, 1490, 1405, 1370, 1240, 1170, 1090, 1065, 1050. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29, 1.33 (2*d*, $J = 7$, 7, CH_3(3.1), rotamers); 1.43 (*s*, *t*-Bu); 3.00, 3.15 (2*s*, CH_3–N(2.2), rotamers); 3.93, 4.37 (*AB*, $J = 18$, 2 H–C(2.2)); 4.59, 4.71 (*m*, H–C(2.1), rotamers); 5.67, 5.73 (2*d*, $J = 8$, H–N(2.1), rotamers); 8.21 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.42, (CH_3(3.1)); 28.36 ((*C*H$_3$)$_3$C); 36.45 (CH_3–N(2.2)); 46.35 (CH(2.1)); 49.71 (CH_2(2.2)); 79.93 ((CH$_3$)$_3$*C*); 155.47 (*t*-BuO*C*O); 172.06 (C(1.1)); 174.26 (C(1.2)). FAB-MS: 283.3 (22, $[M+23]^+$, $C_{11}H_{20}N_3O_5Na^+$), 261.4 (71, $[M+1]^+$, $C_{11}H_{21}N_2O_5^+$), 205.3 (100, $C_7H_{13}N_2O_5^+$), 161.2 (75, $C_6H_{13}N_2O_3^+$), 89.6 ($C_3H_8NO_2^+$).

Boc-Ala-MeAla-OCH$_2$Ph (**3a**). To a soln. of Boc-Ala-OH (1.9 g, 10 mmol) and *N*-methylmorpholine (2.3 ml, 21 mmol) in $CHCl_3$ (40 ml), pivaloyl chloride (1.4 ml, 11 mmol) was added at −20° within 30 min. After 6 h stirring at −20°, a soln. of *N*-methylalanine benzyl ester (2.1 g, 10.5 mmol) in $CHCl_3$ (10 ml) was added slowly. After additional 40 h at −20°, the solvent was evaporated and the residue dissolved in Et_2O (50 ml) and washed with 0.5N H_2SO_4 and sat. $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt/acetone 10:10:1) gave 2.9 g (79%) of **3a**. TLC: R_f 0.5 (hexane/AcOEt/acetone 10:10:1, anisaldehyde). $[\alpha]_D^{r.t.} = -36.1$ ($c = 1$, $CHCl_3$). IR: 3420, 2980, 2940, 1740, 1710, 1650, 1495, 1450, 1405, 1365, 1210, 1170, 1085, 1050, 1030.

Boc-Ala-MeAla-OH (**3b**). As described for **1b**, with **3a** (2.9 g, 7.9 mmol), EtOH (200 ml), and 10% Pd/C (250 mg; 3 h): 2.2 g (98%) of **3b**. $[\alpha]_D^{r.t.} = -36.1$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (360 MHz, 180°, (D_6)DMSO): 1.21 (*d*, $J = 7$, CH_3(3.2)); 1.33 (*d*, $J = 7$, CH_3(3.1)); 1.40 (*s*, *t*-Bu); 2.90 (*s*, CH_3–N(2.2)); 4.47 (*m*, H–C(2.1)); 4.83 (*q*, $J = 10$, H–C(2.2)); 5.75 (br., NH).

*Boc-Ala-Me-*D*-Ala-OCH$_2$Ph* (**4a**). As described for **3a**, with Boc-Ala-OH (1.9 g, 10 mmol) and *N*-methyl-D-alanine (2.0 g, 10.5 mmol): 3.4 g (93%) of **4a**. TLC: R_f 0.5 (hexane/AcOEt/acetone 10:10:1, anisaldehyde). $[\alpha]_D^{r.t.} = +63.5$ ($c = 1$, $CHCl_3$). IR: identical to that of **3a**.

*Boc-Ala-Me-*D*-Ala-OH* (**4b**). As described for **1b**, with **4a** (3.4 g, 9.3 mmol), EtOH (200 ml), and 10% Pd/C (200 mg; 3 h). The residue was recrystallized twice from CH_2Cl_2/petroleum ether: 2.3 g (91%) of **4b**). M.p. 143.5–144.5°. $[\alpha]_D^{r.t.} = +52$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (360 MHz, 180°, (D_6)DMSO): 1.21 (*d*, $J = 7$, CH_3(3.2)); 1.33 (*d*, $J = 7$, CH_3(3.1)); 1.40 (*s*, *t*-Bu); 2.90 (*s*, CH_3–N(2.2)); 4.47 (*m*, H–C(2.1)); 4.75 (*q*, $J = 10$, H–C(2.2)); 5.75 (br. *s*, NH).

Boc-Gly-Sar-MeLeu-OCH$_2$Ph (**5a**). A soln. of **1b** (5.66 g (23 mmol) and Et(i-Pr)$_2$N (8.0 ml, 46.7 mmol) in CH_2Cl_2 (80 ml) was cooled to −18°. After addition of BOP-Cl (6.53 g, 25.7 mmol) and stirring for 90 min, a soln. of *N*-methylleucine benzyl ester hydrochloride (5.88 g, 21.6 mmol) and Et(i-Pr)$_2$N (3.7 ml, 21.6 mmol) in CH_2Cl_2 (60 ml) was added dropwise at −18° within 1 h. The temp. was then raised to r.t. over night. After evaporation, the crude residue was dissolved in Et_2O and washed with 0.1N H_2SO_4, sat. $NaHCO_3$, and sat. NaCl soln. All aq. solns. were extracted twice with Et_2O. The collected org. solvents were worked up as usual. FC (silica gel) gave 17.60 g (85%) of **5a**. TLC: R_f 0.28 (hexane/AcOEt/acetone 5:5:1, anisaldehyde). $[\alpha]_D^{r.t.} = -30.7$ ($c = 0.94$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, $J = 7$, CH_3(5.3)); 0.94 (*d*, $J = 7$, CH_3(5′.3)); 1.44, 1.45 (2*s*, *t*-Bu, rotamers); 1.45–1.54 (*m*, H–C(4.3)); 1.65–1.79 (*m*, 2 H–C(3.3)); 2.82, 2.88, 2.89 (3*s*, CH_3–N(2.3), rotamers); 2.90, 2.95, 2.98 (2*s*, CH_3–N(2.2), rotamers); 4.02 (br. *s*, 2 H–C(2.1)); 4.05, 4.40 (*AB*, $J = 16$, 2 H–C(2.2)); further signals at 3.77–4.42 from rotamers (H–C(2.1), H–C(2.2), H–C(2.3)); 5.13, 5.14 (2*s*, PhCH_2, rotamers); 5.28, 5.33 (2*d*, $J = 5$, 6, H–C(2.3)); 5.44 (br. *s*, H–N(2.1)); 7.31–7.39 (*m*, 5 H, *Ph*CH$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.40, 21.77 (CH_3(5.3)); 23.04, 23.14 (CH_3(5′.3)); 24.62, 25.00 (CH(4.3)); 28.36 (CH_3)$_3$C); 30.58 (CH_3–N(2.3)); 35.17 (CH_3–N(2.2)); 37.09, 37.77 (CH_2(3.3)); 42.28 (CH_2(2.1)); 49.50, 49.55 (CH_2(2.2)); 54.85, 57.39 (CH(2.3)); 66.91 (Ph*C*H$_2$); 79.56 ((CH$_3$)$_3$*C*); 128.17, 128.38, 128.61 (5CH, *Ph*CH$_2$); 135.54 (1C, *Ph*CH$_2$); 155.78 (*t*-BuO*C*O); 168.47 (C(1.1)); 169.13 (C(1.2)); 171.49 (C(1.3)).

Boc-Gly-Sar-MeLeu-OH (**5b**). As described for **1b**, with **5a** (7.9 g, 17.1 mmol), EtOH (200 ml), and 10% Pd/C (405 mg; 15 h): 6.3 g (99%) of **5b**. $[\alpha]_D^{r.t.} = -32.6$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*d*, $J = 7$, CH_3(5.3)); 0.92 (*d*, $J = 7$, CH_3(5′.3)); 1.41 (*s*, *t*-Bu); 1.4–1.5 (*m*, H–C(4.3)); 1.67–1.78 (*m*, 2 H–C(3.3)); 2.84, 2.91 (2*s*, CH_3–N(2.3), rotamers); 2.96, 2.99, 3.02 (3*s*, CH_3–N(2.2), rotamers); 4.03 (*m*, 2 H–C(2.1)); 4.25 (*d*, $J = 4$, 2 H–C(2.2)); further signals at 3.8–4.54 from rotamers (H–C(2.1), H–C(2.2)); 5.15–5.23 (2*d*, $J = 6$, 6, H–C(2.3)); 5.59–5.69 (*m*, H–N(2.1)); 9.12 (br. *s*, COOH). ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 0.81–0.94 (*m*, CH_3(5.3), CH_3(5′.3)); 1.37 (*s*, *t*-Bu); 1.35–1.50 (*m*, H–C(4.3)); 1.53–1.75 (*m*, 2 H–C(3.3)); 2.68–2.91 (*m*, 2CH_3N); 3.2–3.5 (br. *s*, OH–C(1.3)); 3.56–3.82 (*m*, 2 H–C(2.1)); 4.21–4.34 (*m*, 2 H–C(2.2)); 4.97–5.04 (*m*, H–C(2.3)); 6.65–6.73 (*m*, H–N(2.1)). ^{1}H-NMR (80 MHz, 150°, (D$_6$)DMSO): 0.90 (*d*, $J = 6$, CH_3(5.3)); 0.93 (*d*, $J = 6$, CH_3(5′.3)); 1.38 (*s*, *m*, *t*-Bu, H–C(4.3)); 1.5–1.75 (*m*, 2 H–C(3.3)); 2.87, 2.89 (2*s*, 2CH_3N); 3.75 (*d*, $J = 5$, 2 H–C(2.1)); 4.20 (*s*, 2 H–C(2.2)); 4.80 (*t*, $J = 8$, H–C(2.3)); 5.8–6.1 (*m*, H–N(2.1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.24, 21.39 (CH_3(5.3)); 23.12, 23.16 (CH_3(5′.3)); 24.69, 25.04 (CH(4.3)); 28.35 ((CH_3)$_3$C); 30.78 (CH_3–N(2.3)); 35.51 (CH_3–N(2.2)); 36.99 (CH_2(3.3)); 42.28 (CH_2(2.1)); 49.77 (CH_2(2.2)); 54.99 (CH(2.3)); 79.77 ((CH$_3$)$_3$*C*); 156.06 (*t*-BuO*C*O); 168.88 (C(1.1)); 169.76 (C(1.2)); 174.44 (C(1.3)). FAB-MS: 396.3 (25, $[M + 23]^+$, $C_{17}H_{31}N_3O_6Na^+$), 374.3 (13, $[M + 1]^+$, $C_{17}H_{32}N_3O_6^+$), 318.2 (22, $C_{12}H_{24}N_3O_6^+$), 274.4 (26, $C_{12}H_{24}N_3O_4^+$), 229.4 (17, $C_{11}H_{23}N_3O_2^+$ and $C_{10}H_{17}N_2O_4^+$), 217.4 (27, $C_{10}H_{21}N_2O_3^+$), 173.3 (100, $C_6H_9N_2O_4^+$), 146.2 (45, $C_7H_{16}NO_2^+$), 129.0 (67, $C_5H_9N_2O_2^+$), 99.8 (50), 56.2 (98, $C_4H_8^+$). Anal. calc. for $C_{17}H_{31}N_3O_6$: C 54.68, H 8.37, N 11.25; found: C 54.40, H 8.40, N 11.21.

Boc-Ala-Sar-Sar-OCH$_2$Ph (**6a**). As described for **5a**, with **2b** (12.77 g, 49.1 mmol), Et(i-Pr)$_2$N (23.4 ml, 136.7 mmol), CH_2Cl_2 (250 ml), BOP-Cl (19.2 g, 75.4 mmol), sarcosine benzyl ester toluene-4-sulfonate (22.8 g, 64.9 mmol), Et(i-Pr)$_2$N (11 ml, 64.3 mmol), and CH_2Cl_2 (180 ml; within 90 min). FC (silica gel) gave 17.60 g (85%) of **6a**. TLC: R_f 0.38 (AcOEt, anisaldehyde). $[\alpha]_D^{r.t.} = -3.3$ ($c = 0.94$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.26, 1.35 (2*d*, $J = 7$, 7, CH_3(3.1), rotamers); 1.42, 1.43 (2*s*, *t*-Bu, rotamers); 3.06 (*s*, CH_3–N(2.2) or CH_3–N(2.3)); 3.11 (*s*, CH_3–N(2.2) or CH_3–N(2.3)); further signals at 2.90–3.08 from rotamers (CH_3–N(2.2), CH_3–N(2.3)); 3.99, 4.51 (*AB*, $J = 16$, 2 H–C(2.2)); 4.08, 4.26 (*AB*, $J = 17$, 2 H–C(2.3)); further signals at 3.86–4.61 from rotamers (H–C(2.2), H–C(2.3)); 4.64–4.74 (*m*, H–C(2.1)); 5.16, 5.20 (2*s*, PhCH_2, rotamers); 5.40–5.50 (*m*, H–N(2.1)); 7.32–7.39 (*m*, 5 H, *Ph*CH$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.84 (CH_3(3.1)); 28.37 ((CH_3)$_3$C); 35.67, 36.24 (CH_3–N(2.2), CH_3–N(2.3)); 46.38 (CH(2.1)); 49.26, 49.66 (CH_2(2.2), CH_2(2.3)); 67.08, 67.52 (Ph*C*H$_2$); 79.48 ((CH$_3$)$_3$*C*); 128.35, 128.49, 128.53, 128.64, 128.76, (5CH, *Ph*CH$_2$); 135.24 (1C, *Ph*CH$_2$); 155.10 (*t*-BuO*C*O); 168.27, 168.87 (C(1.1), C(1.2)); 173.48 (C(1.3)).

Boc-Ala-Sar-Sar-OH (**6b**). As described for **1b**, with **6a** (17.5 g, 41.6 mmol), EtOH (300 ml), and 10% Pd/C (410 mg; 16 h): 13.9 g (99%) of **6b**. $[\alpha]_D^{r.t.} = -5.2$ ($c = 0.93$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*d*, $J = 7$, CH_3(3.1)); 1.42 (*s*, *t*-Bu); 2.93–3.10 (*m*, CH_3–N(2.2), CH_3–N(3.2)); 3.84–4.60 (*m*, 2 H–C(2.3)); 4.06, 4.11 (2*s*, 2 H–C(2.2), rotamers); 4.69 (*m*, H–C(2.1)); 5.57 (*m*, H–N(2.1)). ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 1.06, 1.15 (2*d*, $J = 5$, 7, CH_3(3.1), rotamers); 1.36 (*s*, *t*-Bu); 2.74–3.02 (*m*, CH_3–N(2.2), CH_3–N(2.3)); 3.33 (br. *s*, COOH); 3.76–4.67 (*m*, H–C(2.1), 2 H–C(2.2), 2 H–C(2.3)); 6.48–6.93 (*m*, H–N(2.1)). ^{1}H-NMR (80 MHz, 150°, (D$_6$)DMSO): 1.22 (*d*, $J = 6$, CH_3(3.1)); 1.44 (*s*, *t*-Bu); 2.95 (br. *s*, CH_3–N(2.2), CH_3–N(2.3)); 4.10 (*s*, 2 H–C(2.2)); 4.0–4.6 (*m*, H–C(2.1), 2 H–C(2.3)); 6.25 (*m*, H–N(2.1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.76 (CH_3(3.2)); 28.37 ((CH_3)$_3$); 35.72, 36.47 (CH_3–N(2.2), CH_3–N(2.3)); 46.44 (CH(2.1)); 49.49, 49.57 (CH_2(2.2), CH_2(2.3)); 79.77 ((CH$_3$)$_3$*C*); 155.39 (*t*-BuO*C*O); 168.43 (C(1.1)); 171.36 (C(1.2)); 174.15 (C(1.3)). FAB-MS: 354.3 (23, $[M + 23]^+$, $C_{14}H_{25}N_3O_6Na^+$), 332.3 (44, $[M + 1]^+$, $C_{14}H_{26}N_3O_6^+$), 276.4 (26, $C_{10}H_{18}N_3O_5^+$), 243.4 (11, $C_{11}H_{19}N_2O_4^+$), 232.4 (41,

$C_9H_{18}N_3O_4^+$), 187.3 (100, $C_7H_{11}N_2O_4^+$ and $C_8H_{17}N_3O_2^+$), 161.2 (68, $C_6H_{13}N_2O_3^+$), 143.1 (38, $C_6H_{11}N_2O_2^+$), 89.6 (26, $C_3H_7NO_2^+$), 56.2 (76, $C_4H_8^+$). Anal. calc. for $C_{14}H_{25}N_3O_6$: C 50.75, H 7.60, N 12.68; found: C 50.54, H 7.68, N 12.57.

Boc-Ala-Sar-MeLeu-OCH$_2$Ph (**7a**). As described for **5a**, with **2b** (10.4 g, 40.0 mmol), Et(i-Pr)$_2$N (13.7 ml, 80.0 mmol), CH_2Cl_2 (150 ml), BOP-Cl (11.2 g, 44.0 mmol, 1 h), *N*-methylleucine benzyl ester hydrochloride (10.3 g, 37.9 mmol), Et(i-Pr)$_2$N (6.5 ml, 38 mmol), and CH_2Cl_2 (100 ml, within 3.5 h). Recrystallization from Et_2O/hexane yielded 16.70 g (92%) of **7a**. M.p. 55.8°. $[\alpha]_D^{r.t.} = -30.7$ ($c = 1.05$, $CHCl_3$). IR: 3420, 2960, 1735, 1710, 1665, 1650, 1480, 1405, 1400, 1365, 1300, 1210, 1370. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*d*, $J = 7$, CH_3(5.3)); 0.92 (*d*, $J = 7$, CH_3(5′.3)); 1.33 (*d*, $J = 7$, CH_3(3.1)); 1.42 (*s*, *t*-Bu); 1.45–1.60 (*m*, H–C(4.3)); 1.64–1.84 (*m*, 2 H–C(3.3)); 2.80–2.88 (2*s*, CH_3–N(2.3), rotamers); 3.02, 3.07 (2*s*, CH_3–N(2.2), rotamers); 3.79, 4.58 (*AB*, $J = 16$, 2 H–C(2.2)); 4.66 (*m*, H–C(2.1)); further signals at 3.91–4.43 from rotamers (H–C(2.1), H–C(2.2), H–C(2.3)); 5.12 (*s*, PhCH_2); 5.29–5.34 (2*d*, $J = 6$, 6, H–C(2.3)); 5.43 (br. *d*, $J = 8$, H–N(2.1)); 7.33 (*s*, 5 H, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.71 (CH_3(3.1)); 21.39 (CH_3(5.3)); 23.15 (CH_3(5′.3)); 24.99 (CH(4.3)); 28.39 ((*C*H$_3$)$_3$C); 30.48 CH_3–N(2.3)); 36.26 (CH_3–N(2.2)); 37.10 (CH_2(3.3)); 46.37 (CH(2.1)); 49.53 (CH_2(2.2)); 54.74 (CH(2.3)); 66.88 (PhCH_2); 79.46 ((CH$_3$)$_3$*C*); 128.16, 128.35, 128.61 (5 CH, *Ph*CH_2); 135.59 (1 C, *Ph*CH_2); 155.13 (*t*-BuO*C*O); 168.52 (C(1.1)); 171.58 (C(1.2)); 173.38 (C(1.3)). Anal. calc. for $C_{25}H_{39}N_3O_6$: C 62.87, H 8.23, N 8.80; found: C 62.52, H 8.25, N 8.80.

Boc-Ala-Sar-MeLeu-OH (**7b**). As described for **1b**, with **7a** (13.2 g, 27.6 mmol), EtOH (280 ml), and 10% Pd/C (561 mg; 5.5 h): 10.7 g (99%) of **7b**. $[\alpha]_D^{r.t.} = -38.3$ ($c = 1$, $CHCl_3$). IR: 3410, 2980, 1710, 1670, 1650, 1485, 1410, 1370, 1300, 1240, 1170, 1100, 1060, 1050, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, $J = 7$, CH_3(5.3)); 0.95 (*d*, $J = 7$, CH_3(5′.3)); 1.34 (*d*, $J = 7$, CH_3(3.1)); 1.43 (*s*, *t*-Bu); 1.45–1.60 (*m*, H–C(4.3)); 1.70–1.79 (*m*, 2 H–C(3.3)); 2.85, 2.93, 2.96 (3*s*, CH_3–N(2.3), rotamers); 2.97, 3.14, 3.17 (3*s*, CH_3–N(2.2), rotamers); 3.95, 4.52 (*AB*, $J = 16$, 2 H–C(2.2)); 4.70 (*m*, H–C(2.1)); 5.22 (*d*, $J = 6$, H–C(2.3)); 5.27 (*d*, $J = 6$, H–C(2.3)); further signals at 3.68–5.93 from rotamers (H–C(2.1), H–C(2.2), H–C(2.3)); 5.64, 5.70, 5.91 (3*d*, $J = 8$, H–N(2.1)); 8.72 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.52 (CH_3(3.1)); 21.37, 21.86 (CH_3(5.3)); 23.05, 23.18 (CH_3(5′.3)); 25.01 (CH(4.3)); 28.37 ((*C*H$_3$)$_3$C); 30.75 (CH_3–N(2.3)); 36.55 (CH_3–N(2.2)); 36.97 (CH_2(3.3)); 46.38 (CH(2.1)); 49.83 (CH_2(2.2)); 54.89, 57.14 (CH(2.3)); 79.65 ((CH$_3$)$_3$*C*); 155.32 (*t*-BuO*C*O); 168.82 (C(1.1)); 172.95, 173.89 (C(1.2)); 174.47, 174.69 (C(1.3)). FAB-MS: 410.3 (6, $[M + 23]^+$, $C_{18}H_{22}N_3O_6Na^+$), 388.3 (15, $[M + 1]^+$, $C_{18}H_{23}N_3O_6^+$), 332.3 (5, $C_{14}H_{26}N_3O_6^+$), 288.4 (23, $C_{13}H_{26}N_3O_4^+$), 243.4 (9, $C_{12}H_{25}N_3O_2^+$), 217.4 (35, $C_{10}H_{21}N_2O_3^+$), 187.3 (27, $C_9H_{17}NO_3^+$), 146.2 (17, $C_7H_{16}NO_2^+$), 99.5 (18), 55.4 (100, $C_4H_7^+$).

Boc-Ala-MeAla-MeLeu-OCH$_2$Ph (**8a**). As described for **3a**, with **3b** (1.0 g, 3.6 mmol), *N*-methylmorpholine (0.9 ml, 7.7 mmol), $CHCl_3$ (20 ml), pivaloyl chloride (0.5 ml, 4.1 mmol) *N*-methylleucine benzyl ester (0.9 g, 3.8 mmol) and $CHCl_3$ (5 ml; 18 h). Drying ($MgSO_4$), evaporation, and FC (hexane/AcOEt/acetone, 10:10:1) gave 1.0 g (53%) of **8a**. TLC: R_f 0.30 (hexane/AcOEt/acetone 10:10:1, anisaldehyde). ^{1}H-NMR (300 MHz, 150°, (D$_6$)DMSO): 0.91 (*d*, $J = 6.4$, CH_3(5.3)); 0.94 (*d*, $J = 6.5$, CH_3(5′.3)); 1.18, 1.21 (2*d*, $J = 6.8$, CH_3(3.1), CH_3(3.2)); 1.44–1.79 (*m*, 2 H–C(3.3), H–C(4.3)); 1.42 (*s*, *t*-Bu); 2.86, 2.88 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 4.43 (*m*, H–C(2.1)); 5.15 (*s*, PhCH_2); 4.99 (*m*, H–C(2.3)); 5.33 (*m*, H–C(2.2)); 6.07 (br. *s*, H–N(2.1)); 7.36 (*m*, 5 H, *Ph*CH_2).

Boc-Ala-MeAla-MeLeu-OH (**8b**). As described for **1b**, with **8a** (1.0 g, 2.2 mmol), EtOH (200 ml), and 10% Pd/C (100 mg; 4 h): 0.75 g (95%) of **8b**. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.80–1.05 (*m*, CH_3(5.3), CH_3(5′.3)); 1.12–1.39 (*m*, CH_3(3.1), CH_3(3.2)); 1.40 (*s*, *m*, *t*-Bu, H–C(4.3)); 1.60–1.90 (*m*, 2 H–C(3.3)); 2.80, 2.87, 2.95 (3*s*, CH_3–N(2.2), CH_3–N(2.3), rotamers); 4.38–4.70 (*m*, H–C(2.1)); 5.36–5.80 (*m*, H–C(2.2), H–C(2.3)); 9.45 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.05 (CH_3(3.2)); 18.55 (CH_3(3.1)); 21.09 (CH_3(5.3)); 23.26 (CH_3(5′.3)); 25.04 (CH(4.3)); 28.32 ((*C*H$_3$)$_3$C); 29.86 (CH_3–N(2.3)); 31.33 (CH_3–N(2.2)); 36.95 (CH_2(3.3)); 46.61 (CH(2.1)); 49.48 (CH(2.2)); 55.06 (CH(2.3)); 79.66 ((CH$_3$)$_3$*C*); 155.02 (*t*-BuO*C*O); 171.85, 172.92 (C(1.1), C(1.2)); 174.54 (C(1.3)).

*Boc-Ala-Me-*D*-Ala-MeLeu-OCH$_2$Ph* (**9a**). As described for **3a**, with **4b** (1.0 g, 3.6 mmol) *N*-methylmorpholine (0.9 ml, 7.7 mmol), $CHCl_3$ (20 ml), pivaloyl chloride (0.5 ml, 4.1 mmol), *N*-methylleucine benzyl ester (0.9 g, 3.8 mmol), and $CHCl_3$ (5 ml; 18 h). FC (hexane/AcOEt/acetone 10:10:1) gave 0.93 g (52%) of **9a**. TLC: R_f 0.30 (hexane/AcOEt/acetone 10:10:1, anisaldehyde). ^{1}H-NMR (300 MHz, 150°, (D$_6$)DMSO): 0.91 (*d*, $J = 6$, CH_3(5.3)); 0.93 (*d*, $J = 6$, CH_3(5′.3)); 1.18, 1.21 (2*d*, $J = 7$, CH_3(3.1), CH_3(3.2)); 1.42 (*s*, *t*-Bu); 1.56–1.80 (*m*, 2 H–C(3.3), H–C(4.3)); 2.85, 2.87 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 4.44–4.54 (*m*, H–C(2.1)); 4.97–5.00 (*m*, H–C(2.3)); 5.15 (*s*, PhCH_2); 5.33 (*m*, H–C(2.2)); 6.06 (br. *s*, H–N(2.1)); 7.36 (*m*, 5 H, *Ph*CH_2).

*Boc-Ala-Me-*D*-Ala-MeLeu-OH* (**9b**). As described for **1b**, with **9a** (1 g, 2.2 mmol), EtOH (200 ml), and 10% Pd/C (100 mg, 4 h): 0.75 g (95%) of **9b**. ^{1}H-NMR (80 MHz, $CDCl_3$): identical with ^{1}H-NMR of **8b**. ^{13}C-NMR (75 MHz, $CDCl_3$): 14.39 (CH_3(3.2)); 18.01 (CH_3(3.1)); 21.46 (CH_3(5.3)); 23.27 (CH_3(5′.3)); 24.91 (CH(4.3)); 28.32

((CH_3)$_3$C); 29.94 (CH_3–N(2.3)); 30.45 (CH_3–N(2.2)); 36.67 (CH_2(3.3)); 46.57 (CH(2.1)); 50.15 (CH(2.2)); 54.83 (CH(2.3)); 79.91 ((CH_3)$_3$*C*); 155.39 (*t*-BuO*C*O); 170.77, 172.54, 173.83, (C(1.1), C(1.2), C(1.3)).

Boc-Ala-Sar-MePhe-OCH$_2$Ph (**10a**). A soln. of **2b** (5.2 g, 20.0 mmol) and Et(i-Pr)$_2$N (7.5 ml, 43.8 mmol) in CH_2Cl_2 (100 ml) was cooled to 0° and BOP-Cl (5.6, 22.0 mmol) added. After 1 h, *N*-methylphenylalanine benzyl ester (5.9 g, 22 mmol) was added, the temp. raised to r.t., and the soln. stirred for 80 h. Workup as described for **5a**. FC (hexane/AcOEt/acetone 5:5:1) gave 4.7 g (45%) of **10a**. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.29 (*d*, *J* = 5, CH_3(3.1)); 1.43 (*s*, *t*-Bu); 2.68, 2.78, 2.87 (3*s*, CH_3–N(2.2), CH_3–N(2.3), rotamers); 3.00–5.50 (*m*, 2 PhC*H*$_2$, H–C(2.1), 2 H–C(2.2), H–C(2.3), H–N(2.1)); 7.23, 7.36 (2*s*, 2 *Ph*CH$_2$). ^{13}C-NMR (20 MHz, $CDCl_3$): 18.68 (CH_3(3.1)); 28.22 ((CH_3)$_3$C); 32.10 (CH_3–N(2.3)); 34.55 (PhCH$_2$); 35.40 (CH_3–N(2.2)); 46.27 (CH(2.3)); 49.20 (CH_2(2.2)); 58.82 (CH(2.1)); 79.25 ((CH_3)$_3$*C*); 126.6, 127–129 (2 *Ph*CH$_2$); 154.84 (*t*-BuO*C*O); 172.98 (C(1.3)).

Boc-Ala-Sar-MePhe-OH (**10b**). As described for **1b**, with **10a** (4.6 g, 9 mmol), EtOH (300 ml), and 10% Pd/C (200 mg; 16 h): 3.1 g (81%) of **10b**. $[\alpha]_D^{r.t.} = -70.6$ (*c* = 1.38, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 (*d*, *J* = 6.9, CH_3(3.1)); 1.43 (*s*, *t*-Bu); 2.69–2.85, 2.90–3.13 (2*m*, CH_3–N(2.1), CH_3–N(2.2)); 3.31–3.50 (*m*, H–C(2.1)); 4.00, 4.20 (*AB*, *J* = 16, 2 H–C(2.2)); 4.51–4.69 (2*m*, PhC*H*$_2$); 5.11–5.73 (2*m*, H–N(2.1), H–C(2.3)); further signals at 3.31–5.73 from rotamers (H–C(2.1), H–C(2.2), H–C(2.3)); 7.16–7.35 (*m*, *Ph*CH$_2$); 7.71 (br. *s*, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.64 (CH_3(3.1)); 28.36 ((CH_3)$_3$C); 29.85 (CH_3–N(2.3)); 34.42 (PhCH$_2$); 35.97 (CH_3–N(2.2)); 46.38 (CH(2.3)); 49.71 (CH_2(2.2)); 61.41 (CH(2.1)); 79.68 ((CH_3)$_3$*C*); 126.79, 128.59, 128.80, 128.98, 129.12, 137.12 (5CH, 1C, *Ph*CH$_2$); 155.29, 155.41 (*t*-BuO*C*O); 168.07, 168.36 (C(1.1)); 171.3, 172.76 (C(1.2)); 173.86 (C(1.3)).

Boc-Ala-Sar-MeVal-OCH$_2$Ph (**11a**). As described for **10a**, with **2b** (4.1 g, 15.8 mmol), Et(i-Pr)$_2$N (3 ml, 18 mmol), CH_2Cl_2 (300 ml; 0°) BOP-Cl (4.4 g, 17 mmol; 1 h), *N*-methylvaline benzyl ester hydrochloride (3.7 g, 15 mmol) Et(i-Pr)$_2$N (3 ml, 18 mmol), and CH_2Cl_2 (50 ml, within 3.5 h). Workup with AcOEt and sat. $KHSO_4$ soln., H_2O, 1N $KHCO_3$ and sat. NaCl soln. and evaporation gave 5.75 g (80%) of **11a**. TLC: R_f 0.61 (hexane/AcOEt 2:1, anisaldehyde). $[\alpha]_D^{r.t.} = -66.4$ (*c* = 1.57, $CHCl_3$). IR: 3430, 3040, 2980, 2940, 1730, 1710, 1650, 1490, 1415, 1370, 1300, 1170, 1130, 1090, 1055. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.87 (br. *d*, *J* = 5.5, CH_3(4.3)); 0.97 (br. *d*, *J* = 5.5, CH_3(4'.3)); 1.23–1.57 (*m*, CH_3(3.1), H–C(3.3)); 1.43 (*s*, *t*-Bu); 2.85, 2.93 (2*s*, CH_3–N(2.3), rotamers); 3.03, 3.06 (2*s*, CH_3–N(2.2), rotamers); 3.57–5.00 (rotamers, H–C(2.1), H–C(2.3), 2 H–C(2.2)); 5.01 (*s*, PhC*H*$_2$); 5.35 (br. *s*, H–N(2.1)); 7.30 (*s*, 5 H, *Ph*CH$_2$).

Boc-Ala-Sar-MeVal-OH (**11b**). As described for **1b**, with **11a** (5.8 g, 12.7 mmol) EtOH (250 ml), and 10% Pd/C (570 mg; 16 h): 4.14 g (87%) **11b**. TLC: R_f 0.03 (hexane/AcOEt 1:2, anisaldehyde). $[\alpha]_D^{r.t.} = -76.3$ (*c* = 1.31, $CHCl_3$). IR: 3430, 2980, 2940, 1705, 1650, 1485, 1420, 1395, 1370, 1300, 1170, 1090, 1060. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.83–1.00 (*m*, CH_3(4.3), CH_3(4'.3)); 1.06 (*d*, *J* = 5.5, CH_3(3.1)); 1.43 (*s*, *t*-Bu, H–C(3.3)); 2.88, 3.01 (2*s*, CH_3–N(2.3), rotamers); 3.17 (*s*, CH_3–N(2.2)); 3.67–5.00 (rotamers, H–C(2.1), H–C(2.3), 2 H–C(2.2)); 5.73, 6.03 (2*d*, *J* = 6, H–N(1.2), rotamers); 8.70 (br. *s*, COOH). ^{1}H-NMR (80 MHz, 80°, $CDCl_3$): 0.91 (*d*, *J* = 7, CH_3(4.3)); 1.03 (*d*, *J* = 7, CH_3(4'.3)); 1.29 (*d*, *J* = 7, CH_3(3.1)); 1.41 (*s*, *t*-Bu, H–C(3.3)); 2.92 (*s*, CH_3–N(2.3)); 3.08 (*s*, CH_3–N(2.2)); 3.13–4.78 (rotamers, H–C(2.1), H–C(2.3), 2 H–C(2.2)); 5.47 (*d*, *J* = 7, H–N(2.1)); 8.59 (br. *s*, COOH).

5. *Alkylations. Boc-Ala-Me-*DL*-Ala-MeLeu-OMe* (**8c**/**9c**). With 2 equiv. of LDA: A soln. of **7b** (0.5 g, 1.3 mmol) in THF (20 ml) was cooled to –70° and treated with 3 mmol of a precooled LDA soln. (generated as described in *Exper. 2*). After 2 h, MeI (0.5 ml, 8 mmol) was added and the resulting slurry stirred for 16 h at –70°. TLC: no product formation.

With 3 equiv. of LDA: A soln. of **7b** (497 mg, 1.3 mmol) in THF (20 ml) was cooled to –70° and treated with 4.2 mmol of precooled LDA soln. (see *Exper. 2*). After 2 h stirring at –70°, MeI (0.5 ml, 8 mmol) was added and the slurry stirred over night at –70°. After hydrolysis at –78° with 1 ml of a pH 7 buffer, the mixture was warmed to r.t. and partitioned between Et_2O and 0.5N H_2SO_4. Washing with 3% aq. $Na_2S_2O_3$ soln., drying ($MgSO_4$), and esterification with diazomethane (see *Exper. 2*) gave, after FC (hexane/AcOEt/acetone 5:5:1), 190 mg (41%) of **8c**/**9c**. ^{13}C-NMR: **8c**/**9c** 1:1.7.

With 3 equiv. of LDA and 5 equiv. of LiCl: A soln. of **7b** (0.5 g, 1.3 mmol) and dry LiCl (275 mg, 6.5 mmol) was deprotonated with LDA (4.2 mmol) (*Exper. 2*). After 2 h stirring at –70°, MeI (0.5 ml, 8 mmol) was added and the soln. stirred overnight at –70°. After the same workup, esterification, and chromatography as above, 249 mg (50%) of **8c**/**9c** and 127 mg (25%) of **7c** resulted. ^{13}C-NMR: **8c**/**9c** 1:3.2.

With 3 equiv. of LDA and additional deprotonation of (i-Pr)$_2$NH with BuLi: A soln. of **7b** (0.51, 1.3 mmol) was deprotonated with LDA (4.2 mmol) (*Exper. 2*). After 2 h at –70°, (i-Pr)$_2$NH was again deprotonated with BuLi (3.2 ml). After 1 additional h, MeI (0.5 ml, 8 mmol) was added and the soln. stirred overnight at –70°. After the same workup, esterification, and chromatography as above, 227 mg (42%) of **8c**/**9c** resulted.

With 3 equiv. of LDA, 6 equiv. of LiCl, and additional deprotonation of $(i\text{-Pr})_2NH$ with BuLi: According to *Exper. 2*, **7b** (495 mg, 1.3 mmol) was deprotonated with LDA (4.2 mmol) and alkylated with MeI (0.5 ml, 8 mmol) in the presence of dry LiCl (336 mg, 8 mmol). After the same workup, esterification, and chromatography as above, 424 mg (80%) of **8c**/**9c** resulted. GC and ^{13}C-NMR: **8c**/**9c** 1:3.7.

All spectra were identical to those of authentic samples (obtained by esterification of **8b** and **9b** with diazomethane).

Transmetalation: Boc-Ala-MeAla-MeLeu-OMe (**8c**/**9c**). A soln. of **7b** (510 mg, 1.3 mmol) and LiCl (400 mg, 9.4 mmol) in abs. THF (20 ml) was cooled to −70°. After the addition of LDA (4.2 mmol) and 2 h of stirring, $MgBr_2 \cdot Et_2O$[30]) (1.6 ml) was added, whereupon $MgBr_2$ immediately precipitated. Warming up to −40° gave a stirrable suspension which remained stirrable even at −70°. After 1 additional h of stirring, the $(i\text{-Pr})_2NH$ formed was deprotonated with BuLi (2.8 ml). Then, MeI (0.5 ml, 1.14 g, 8 mmol) was added and the mixture stirred overnight. The reaction was stopped by the addition of 1 ml of pH 7 buffer and the soln. extracted with Et_2O. The combined org. phase was washed with buffer (pH 7), 1N H_2SO_4, and sat. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The crude product was esterified with diazomethane and purified by FC (hexane/AcOEt/acetone 5:5:1): 50 mg (10%) of **8c**/**9c**. Spectral data: identical with those of authentic samples.

*Boc-Abu-Me-*DL*-Ala-MeLeu-Val-MeLeu-Ala-OMe* (**13c**/**14c**). A soln. of dry LiCl (112 mg, 2.65 mmol) and **12b** (0.35 g, 0.5 mmol) in THF (12 ml) was cooled to −75° and deprotonated by the addition of 1.56N BuLi/hexane (1.6 ml). After 75 min, MeI (0.8 ml, 13 mmol) was added causing immediately a precipitation which dissolved after 10 min. Then, the temp. was raised to −23°. After 4 h, the reaction was stopped by the addition of 2N HCl (5 ml). After the addition of CH_2Cl_2 (50 ml) and H_2O (20 ml), the pH of the soln. was set to 4 with 1N HCl and Na_2CO_3. The aq. layer was extracted with CH_2Cl_2 (3×), the org. layer washed 3× with 70 ml of H_2O which was reextracted with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. The resulting oil was esterified with diazomethane (*Exper. 2*) and **13c**/**14c** separated by FC (pentane/AcOEt 1:2.5): 63.6 mg (0.09 mmol) of **12c**, 191.7 mg (0.26 mmol) of **14c**, and 43.5 mg (0.06 mmol) of **13c**.

12c: TLC: R_f 0.11 (pentane/AcOEt 1:2.5); R_f 0.25 (pentane/AcOEt 1:3). ^1H-NMR (360 MHz, 170°, (D_6)DMSO): 0.84–0.95 (*m*, CH_3(5.3), CH_3(5′.3), CH_3(5.5), CH_3(5′.5), CH_3(4.4), CH_3(4′.4), CH_3(4.1)); 1.24 (*d*, $J = 6$, CH_3(3.6)); 1.39 (*s*, *t*-Bu); 1.47–1.61, 1.67–1.78 (2*m*, 2 H–C(3.1), 2 H–C(3.3), H–C(4.3), 2 H–C(3.5), H–C(4.5)); 2.01–2.10 (*m*, H–C(3.4)); 2.88, 2.92, 2.98 (3*s*, CH_3–N(2.2), CH_3–N(2.3), CH_3–N(2.5)); 4.00–4.12 (br. *m*, H–C(2.6)); 4.15, 4.28 (*AB*, $J = 17$, 2 H–C(2.2)); 4.31–4.38 (*m*, H–C(2.1)); 4.60 (*t*, $J = 7$, H–C(2.4)); 4.79 (*t*, $J = 6$, H–C(2.5)); 4.95 (*t*, $J = 7$, H–C(2.3)); 5.66 (br. *d*, $J = 5$, H–N(2.1)); 6.91–7.07 (2 br. *s*, H–N(2.4), H–N(2.6)).

13c: TLC: R_f 0.32 (pentane/AcOEt 1:2.5); R_f 0.48 (pentane/AcOEt 1:3). $[\alpha]_D^{r.t.} = -163.4$ ($c = 0.585$, $CHCl_3$). ^1H-NMR (360 MHz, 180°, (D_6)DMSO): 0.83–0.95 (*m*, CH_3(5.3), CH_3(5′.3), CH_3(5.5), CH_3(5′.5), CH_3(4.4), CH_3(4′.4), CH_3(4.1)); 1.25 (*d*, $J = 6$, CH_3(3.6)); 1.29 (*d*, $J = 6$, CH_3(3.2)); 1.39 (*s*, *t*-Bu); 1.47–1.58, 1.63–1.80 (2*m*, 2 H–C(3.1), 2 H–C(3.3), H–C(4.3), 2 H–C(3.5), H–C(4.5)); 1.98–2.09 (*m*, H–C(3.4)); 2.84, 2.93, 2.95 (3*s*, CH_3–N(2.2), CH_3–N(2.3), CH_3–N(2.5)); 3.63 (*s*, $COOCH_3$); 4.30–4.41 (*m*, H–C(2.6), H–C(2.1)); 4.61 (*t*, $J = 7$, H–C(2.4)); 4.85–4.95 (*m*, H–C(2.5), H–C(2.3)); 5.32 (*q*, $J = 6$, H–C(2.2)); 5.73 (br. *d*, $J = 5$, H–N(2.1)); 6.88, 7.16 (2 br. *s*, H–N(2.4), H–N(2.6)). FAB-MS: 749.4 (8, $[M + Na]^+$, $C_{36}H_{66}N_6O_9Na^+$), 727.4 (6, $[M + 1]^+$, $C_{36}H_{67}N_6O_9^+$), 624,4 (12, $C_{32}H_{58}N_5O_7^+$), 568.3 (1, $C_{28}H_{50}N_5O_7^+$), 497.3 (4, $C_{25}H_{45}N_4O_6^+$), 398.2 (26, $C_{20}H_{36}N_3O_5^+$), 342.2 (11, $C_{16}H_{28}N_3O_5^+$), 271.1 (18, $C_{13}H_{23}N_2O_4^+$), 215.1 (65, $C_9H_{15}N_2O_4^+$), 100.0 (48), 57.9 (100), 56.9 (53).

14c: TLC: R_f 0.18 (pentane/AcOEt 1:2.5); R_f 0.34 (pentane/AcOEt 1:3). $[\alpha]_D^{r.t.} = -117.1$ ($c = 1.07$, $CHCl_3$). ^1H-NMR (360 MHz, 170°, (D_6)DMSO): 0.82–0.94 (*m*, CH_3(5.3), CH_3(5′.3), CH_3(5.5), CH_3(5′.5), CH_3(4.4), CH_3(4′.4), CH_3(4.1)); 1.23 (*d*, $J = 6$, CH_3(3.6)); 1.28 (*d*, $J = 6$, CH_3(3.2)); 1.38 (*s*, *t*-Bu); 1.47–1.60, 1.63–1.78 (2*m*, 2 H–C(3.1), 2 H–C(3.3), H–C(4.3), 2 H–C(3.5), H–C(4.5)); 1.98–2.09 (*m*, H–C(3.4)); 2.88, 2.91, 2.97 (3*s*, CH_3–N(2.2), CH_3–N(2.3), CH_3–N(2.5)); 3.62 (*s*, $COOCH_3$); 4.32 (*q*, $J = 6$, H–C(2.6)); 4.38 (*q*, $J = 6$, H–C(2.1)); 4.59 (*t*, $J = 7$, H–C(2.4)); 4.78–4.87 (*m*, H–C(2.5)); 4.92 (br. *t*, $J = 6$, H–C(2.3)); 5.28 (*q*, $J = 6$, H–C(2.2)); 5.73 (br. *d*, $J = 5$, H–N(2.1)); 6.89, 7.15 (2 br. *s*, H–N(2.4), H–N(2.6)). FAB-MS: 749.4 (2, $[M + Na]^+$, $C_{36}H_{66}N_6O_9Na^+$), 727.4 (3, $[M + 1]^+$, $C_{36}H_{67}N_6O_9^+$), 627.4 (15, $C_{31}H_{58}N_6O_7^+$), 624,4 (12, $C_{32}H_{58}N_5O_7^+$), 568.3 (3, $C_{28}H_{50}N_5O_7^+$), 497.3 (2, $C_{25}H_{45}N_4O_6^+$), 398.2 (12, $C_{20}H_{36}N_3O_5^+$), 342.2 (9, $C_{16}H_{28}N_3O_5^+$), 271.1 (12, $C_{13}H_{23}N_2O_4^+$), 215.1 (41, $C_9H_{15}N_2O_4^+$), 100.0 (48), 57.9 (100), 56.9 (52).

*Boc-Gly-Me-*DL*-Ala-MeLeu-OMe* (**15**/**16**), *Boc-*DL*-Ala-Sar-MeLeu-OMe* (**7c**/**17**), *and Boc-*DL*-Ala-Me-*DL*-Ala-MeLeu-OMe* (**8c**/**9c**/**18**). With deprotonation of $(i\text{-Pr})_2NH$ with BuLi, no cosolvent; alkylation at −78°: According to *Exper. 2*, LDA (4.37 mmol) was slowly added to **5b** (502 mg, 1.34 mmol) and LiCl (329 mg, 7.76

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[30]) For the generation of $MgBr_2 \cdot Et_2O$, see [56].

mmol). After 2 h, BuLi (3.1 ml, 4.37 mmol) and MeI (0.6 ml, 9.64 mmol) were added slowly. After 15 h of stirring at −78°, the mixture was worked up (additional washing with 0.1N ($Na_2S_2O_3$)): 512 mg of product mixture. Esterification of the crude product (410 mg) and FC (silica gel, hexane/AcOEt 1:10) gave 57 mg (13%) of **15**/**16**, 71 mg (16%) of **7c**/**17**, and 190 mg (46%) of esterified starting material **5c**.

With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at −18°: According to *Exper. 2*, **5b** (489 mg, 1.31 mmol) in THF (25 ml) was deprotonated in the presence of LiCl (353 mg, 8.33 mmol) with LDA (4.23 mmol) at −78°. After 2 h, DMPU (2.5 ml) was added followed by BuLi (3.0 ml, 4.23 mmol) and MeI (0.6 ml, 9.64 mmol). A little later, a viscous oil separated. Upon warming the mixture to −18°, it became homogeneous. Usual workup after 3.5 h gave 1.08 g of product mixture. Esterification of the crude product (976 mg) and FC (silica gel, hexane/AcOEt 1:10) provided 269 mg (62%) of **15**/**16**, 20 mg (4%) of **7c**/**17**, 107 mg (22%) of **8c**/**9c**/**18**, and 36 mg (8%) of esterified starting material **5c**.

15/**16**: TLC: R_f 0.47 (hexane/AcOEt 1:10, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88 (*d*, *J* = 6, CH_3(5.3)); 0.91 (*d*, *J* = 7, CH_3(5′.3)); 1.25 (*d*, *J* = 7, CH_3(3.2)); 1.42 (*s*, *m*, *t*-Bu, H–C(4.3)); 1.54–1.74 (*m*, 2 H–C(3.3)); 2.81, 2.86 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.66 (*s*, CH_3O, further signals of rotamers); 3.96 (*d*, *J* = 4, 2 H–C(2.1)); 5.24 (2*d*, *J* = 6, 6, H–C(2.3)); 5.45–5.56 (*m*, H–C(2.2), H–N(2.1)). ^{1}H-NMR (80 MHz, 180°, (D_6)DMSO): 0.92 (*m*, CH_3(5.3), CH_3(5′.3)); 1.21 (*d*, *J* = 7, CH_3(3.2)); 1.42 (*s*, *t*-Bu); 1.40–1.45 (*m*, H–C(4.3)); 1.65–1.80 (*m*, 2 H–C(3.3)); 2,73, 2.85 (CH_3–N(2.2), CH_3–N(2.3), H_2O); 3.64 (*s*, CH_3O); 3.75 (*d*, *J* = 5, 2 H–C(2.1)); 4.75–6.2 (*m*, H–C(2.2), H–C(2.3), H–N(2.1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.52 (CH_3(3.2)); 21.38 (CH_3(5.3)); 23.02 (CH_3(5′.3)); 24.95 (CH(4.3)); 28.35 ((CH_3)$_3$C); 29.01, 30.52 (CH_3–N(2.2), CH_3–N(2.3)); 36.85 (CH_2(3.3)); 42.52 (CH_2(2.1)); 49.61 (CH(2.2)); 52.22 (CH_3O); 54.74 (CH(2.3)); 79.70 ((CH_3)$_3C$); 155.77 (*t*-BuO*C*O); 168.23–172.53 (C(1.1), C(1.2), C(1.3)). FAB-MS: 424.1 (13, $[M+23]^+$, $C_{19}H_{35}N_3O_6Na^+$), 402.2 (7, $[M+1]^+$, $C_{19}H_{36}N_3O_6^+$), 400.2 (6, $[M-1]^+$, $C_{19}H_{34}N_3O_6^+$), 243.1 (23, $C_{11}H_{19}N_2O_4^+$), 187.0 (80, $C_7H_{11}N_2O_4^+$), 160.1 (37, $C_8H_{18}NO_2^+$), 57.2 (100, $C_4H_9^+$).

7c/**17**. TLC: R_f 0.36 (hexane/AcOEt 1:10, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.88–0.95 (*m*, CH_3(5.3), CH_3(5′.3)); 1.27, 1.34 (2*d*, *J* = 7, 7, CH_3(3.1), rotamers); 1.42 (*s*, *t*-Bu); 1.50 (*m*, H–C(4.3)); 1.72 (*m*, 2 H–C(3.3)); 2.91, 3.11 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.69, 3.74 (2*s*, CH_3O, rotamers); 3.84, 4.58 (*AB*, *J* = 16, *ca.* 1 H, 2 H–C(2.2), L,L-diastereoisomer); 4.10, 4.37 (*AB*, *J* = 16, *ca.* 1 H, 2 H–C(2.2), D,L-diastereoisomer); 4.68 (*m*, H–C(2.1)); 5.28 (2*d*, *J* = 6, 6, H–C(2.3)); 5.45 (*m*, H–N(2.1)). ^{1}H-NMR (80 MHz, 150°, (D_6)DMSO): 3.66 (*s*, CH_3O (only 1*s*)). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.70, *18.91* (CH_3(3.1)); 21.38 (CH_3(5.3)); 23.18 (CH_3(5′.3)); 24.96 (CH(4.3)); 28.37 ((CH_3)$_3$C); 30.44 (CH_3–N(2.3)); 36.38 (CH_3N(2.2)); 37.20 (CH_2(3.3)); 46.36 (CH(2.1)); *49.49*, 49.56 (CH_2(2.2)); 52.19 (CH_3O); 54.49, 54.57 (CH(2.3)); 79.44 ((CH_3)$_3C$); 155.12 (*t*-BuO*C*O); 168.14–173.75 (C(1.1), C(1.2), C(1.3)); signals in italics are not present in the ^{13}C-NMR of **7c** (L,L-diastereoisomer). FAB-MS: 402.1 (52, $[M+1]^+$, $C_{19}H_{36}N_3O_6^+$), 346.1 (7, $C_{15}H_{28}N_3O_6^+$), 302.1 (22, $C_{14}H_{28}N_3O_4^+$), 257.1 (15, $C_{12}H_{21}N_2O_4^+$), 243.1 (22, $C_{11}H_{19}N_2O_4^+$), 231.1 (47, $C_{11}H_{23}N_2O_3^+$), 229.8 (23, $C_{11}H_{21}N_2O_3^+$), 187.0 (100, $C_7H_{11}N_2O_4^+$), 160.1 (67, $C_8H_{18}NO_2^+$), 56.3 (94, $C_4H_8^+$).

8c/**9c**/**18**. TLC: R_f 0.55 (hexane/AcOEt 1:10, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): identical with that of **8c**/**9c**. ^{13}C-NMR (75 MHz, $CDCl_3$): identical with that of **8c**/**9c**. FAB-MS: 416.3 (4, $[M+1]^+$, $C_{20}H_{38}N_3O_6^+$), 271.1 (4, $C_{13}H_{23}N_2O_4^+$), 257.2 (19, $C_{12}H_{21}N_2O_4^+$), 243.2 (8, $C_{12}H_{23}N_2O_3^+$), 201.1 (47, $C_8H_{13}N_2O_4^+$), 160.2 (15, $C_8H_{18}NO_2^+$), 57.3 (100, $C_4H_9^+$).

*Boc-Gly-Me-*DL-*Phe-MeLeu-OMe* (**19**/**20**), *Boc-*DL-*Phe-Sar-MeLeu-OMe* (**21**/**22**). With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at −78°: To a soln. of **5b** (467 mg, 1.25 mmol) and LiCl (380 mg, 8.96 mmol) in THF (20 ml) was slowly added LDA (4.2 mmol) at −78°. After 2.5 h, DMPU (2.0 ml) was added followed by BuLi (3.0 ml, 4.2 mmol) and $PhCH_2Br$ (1.0 ml, 8.41 mmol). After 16.5 h of stirring at −78° and usual workup, the crude product was esterified and purified by FC (hexane/AcOEt 1:2): 42 mg (8%) of **19**/**20**, 90 mg (18%) of **21**/**22**, and 109 mg (27%) of esterified starting material **5c**.

With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at 0°: A soln. of **5b** (454 mg, 1.22 mmol) and LiCl (364 mg, 8.59 mmol) in THF (20 ml) was cooled to −78°. After addition of LDA (4.2 mmol) and 2 h of stirring, DMPU (2.0 ml), BuLi (3.0 ml, 4.2 mmol), and $PhCH_2Br$ (1.0 ml, 8.41 mmol) were slowly added. Then, the mixture was stirred for 6 h at −18° and 30 min at 0°. Usual workup provided 2.03 g of crude product. Esterification of 1.71 g and FC (hexane/AcOEt 1:2) gave 30 mg (6%) of **19**/**20**, 150 mg (31%) of **21**/**22**, and 99 mg (25%) of **5c**.

19/**20**. TLC: R_f 0.51 (hexane/AcOEt 1:2, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.79 (2*d*, *J* = 6, 6, CH_3(5.3), CH_3(5′.3), rotamers); 1.10 (*m*, H–C(4.3)); 1.43 (*s*, *t*-Bu); 1.62 (*m*, 2 H–C(3.3)); 2.76, 2.96 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 2.9, 3.24 (*m*, 2 H–C(3.2)); 3.66 (*s*, CH_3O); 3.85, 3.92 (2*d*, *J* = 4, 4, 2 H–C(2.1)); 5.20 (2*d*, *J* = 5, 6, H–C(2.3)); 5.40 (*m*, H–N(2.1)); 5.73 (*t*, *J* = 5, H–C(2.2)); 7.22 (*m*, 5 H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.24 (CH_3(5.3)); 23.17 (CH_3(5′.3)); 24.63 (CH(4.3)); 28.33 ((CH)$_3$C); 29.53, 30.71 (CH_3–N(2.2),

CH_3–N(2.3)); 35.55 (CH_2(3.2)); 37.71 (CH_2(3.3)); 42.47 (CH_2(2.1)); 52.21 (CH_3O); 54.52, 54.61 (CH(2.2), CH(2.3)); 79.66 ((CH_3)$_3C$); 126.70, 128.37, 129.32 (5 CH, Ph); 136.81 (1 C, Ph); 155.69 (*t*-BuO*C*O); 168.52, 170.09, 171.96 (C(1.1), C(1.2), C(1.3)). FAB-MS: 478.4 (13, $[M+1]^+$, $C_{25}H_{40}N_3O_6^+$), 318.5 (18, $C_{17}H_{22}N_2O_4^+$), 262.1 (52, $C_{13}H_{14}N_2O_4^+$), 218.2 (6, $C_{12}H_{14}N_2O_2^+$), 159.8 (13, $C_8H_{18}NO_2^+$), 55.6 (38, $C_4H_8^+$).

21/22. TLC: R_f 0.34 (hexane/AcOEt 1:2, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*m*, CH_3(5.3), CH_3(5'.3)); 1.36 (*s*, *t*-Bu); 1.43 (*m*, H–C(4.3)); 2.87, 2.97 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.0 (*m*, 2 H–C(3.1)); 3.67 (*s*, CH_3O, further signals of rotamers); 3.80–4.43 (*m*, 2 H–C(2.2)); 4.89 (*m*, H–C(2.1)); 5.28 (*m*, H–C(2.3), H–N(2.1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.34 (CH_3(5.3)); 23.21 (CH_3(5'.3)); 24.95 (CH(4.3)); 28.31 ((CH_3)$_3$C); 30.42 (CH_3–N(2.3)); 36.26 (CH_3–N(2.2)); 37.17 (CH_2(2.2)); 52.19 (CH_3O); 54.45, 54.57 (CH(2.1), CH(2.3)); 79.52 ((CH_3)$_3C$); 126.71, 128.25, 129.71 (5 CH, Ph); 136.32 (1 C, Ph); 155.09 (*t*-BuO*C*O); 168.07–172.41 (C(1.1), C(1.2), C(1.3)). FAB-MS: 478.5 (100, $[M+1]^+$, $C_{25}H_{40}N_3O_6^+$), 378.1 (66, $C_{20}H_{32}N_3O_4^+$), 318.5 (19, $C_{17}H_{22}N_2O_4^+$), 262.1 (89, $C_{13}H_{14}N_2O_4^+$), 230.3 (100, $C_{11}H_{22}N_2O_3^+$), 159.9 (66, $C_8H_{18}NO_2^+$), 55.6 (80, $C_4H_8^+$).

Boc-Ala-Me-DL-*Ala-Sar-OMe* (**23/24**), *Boc-Ala-Sar-Me*-DL-*Ala-OMe* (**25/26**), *and Boc-Ala-Me*-DL-*Ala-Me*-DL-*Ala-OMe* (**27**). With additional deprotonation of (i-Pr)$_2$NH with BuLi, no cosolvent; alkylation at –78°: According to *Exper. 2*, **6b** (549 mg, 1.66 mmol) in THF (30 ml) was deprotonated in the presence of LiCl (587 mg, 13.85 mmol) with LDA (5.57 mmol). After 2 h, BuLi (4.2 ml, 5.57 mmol) and MeI (0.75 ml, 12.0 mmol) were added slowly. After 20 h of stirring at –78° and workup as usual, only 269 mg of product mixture could be isolated. Therefore, the aq. phase was extracted 3× with CH_2Cl_2 resulting in the isolation of additional 204 mg of product mixture. After esterification of 406 mg of the mixture with diazomethane and FC (hexane/AcOEt/acetone 1:10:1), 46 mg (9%) of **23/24**, 87 mg (17%) of **25/26**, 78 mg (17%) of **27**, and 119 mg (23%) of esterified starting material **6c** were isolated.

With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at –18°: To **6b** (489 mg, 1.48 mmol) and LiCl (366 mg, 8.63 mmol) in THF (30 ml), LDA (4.72 mmol) was slowly added, according to *Exper. 2*. After 2 h, DMPU (3.0 ml), BuLi (3.5 ml, 4.72 mmol), and MeI (0.65 ml, 10.44 mmol) were added. After a short time, a viscous oil separated which was dissolved by warming to –18°. After stirring for 3 h at –18° and workup, the crude product (434 mg) was purified by FC (silica gel, hexane/AcOEt/acetone 1:10:1): 29 mg (5%) of **25/26** and 47 mg (9%) of **27**. Combination of the other fractions gave a mixture of **23/24** and **27** which was separated on prep. HPLC (hexane/i-PrOH 9:1): 97 mg of **27** and 63 mg of **23/24**. Total yield: 12% of **23/24**, 5% of **25/26**, and 26% of **27**.

Without deprotonation of (i-Pr)$_2$NH with BuLi, no cosolvent; alkylation at –78°: To a soln. of **6b** (499 mg, 1.50 mmol) and LiCl (264 mg, 6.23 mmol) in THF (20 ml), LDA (4.94 mmol) was slowly added at –78°. Omitting the second deprotonation with BuLi, MeI (0.4 ml, 6.42 mmol) was added after 90 min, working up after 20 h. Separation by prep. HPLC (silica gel, hexane/i-PrOH) gave 26 mg (5%) of **24**, 24 mg (4%) of **23**, 4 mg (1%) of **25/26**, and 168 mg (48%) of esterified starting material (**6c**).

Without deprotonation of (i-Pr)$_2$NH with BuLi, no cosolvent; alkylation at –26°: To a soln. of **6b** (500 mg, 1.51 mmol) and LiCl (259 mg, 6.11 mmol) in THF (20 ml), LDA (4.94 mmol) was slowly added at –78°. After 2 h, MeI (0.4 ml, 6.42 mmol) was added and the temp. held at –78° for 30 min and then at –26° for 17 h. Workup provided two samples which were enriched (*ca.* 65%) with **23** and **24** (82 mg and 91 mg, resp.), as well as 60 mg (12%) of esterified starting material (**6c**); from the usual analysis (degradation, derivatization, and GC analysis) we calculated that **23** and **24** had been formed in a ratio of 1.1:1.

23/24. TLC: R_f 0.44 (hexane/AcOEt/acetone 1:10:1, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.26, 1.29 (2*d*, J = 7, 7, CH_3(3.1), CH_3(3.2), rotamers); 1.42 (*s*, *t*-Bu); 2.98 (*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.70, 3.73 (2*s*, CH_3O, rotamers); 3.94 (*d*, J = 17, 1 H, H–C(2.3)); 4.24 (*d*, J = 17, 1 H, H–C(2.3), further signals of rotamers); 4.61 (*m*, H–C(2.1)); 5.34–5.58 (*m*, H–C(2.2), H–N(2.1)). ^{1}H-NMR (80 MHz, 180°, (D_6)DMSO): 1.22 (*d*, J = 6, CH_3(3.1), CH_3(3.2)); 1.42 (*s*, *t*-Bu); 2.90, 2.95 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 3.67, 3.69 (2*s*, CH_3O, rotamers); 4.05–5.4 (*m*, H–C(2.1), H–C(2.2), 2 H–C(2.3)); 5.95 (br. *m*, H–N(2.1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.22, 14.63 (CH_3(3.2)); 18.29, 18.49 (CH_3(3.1)); 28.28 ((CH_3)$_3$C); 29.94 (CH_3–N(2.3)); 36.26 (CH_3–N(2.2)); 46.55 (CH(2.1)); 48.82, 49.39 (CH(2.2)); 50.01 (CH_2(2.3)); 52.18 (CH_3O); 79.67 ((CH_3)$_3C$); 155.25 (*t*-BuO*C*O); 169.40–172.63 (C(1.1), C(1.2), C(1.3)). FAB-MS: 360.2 (15, $[M+1]^+$, $C_{16}H_{30}N_3O_6^+$), 304.1 (3, $C_{12}H_{22}N_3O_6^+$), 257.1 (44, $C_{12}H_{21}N_2O_4^+$), 215.1 (6, $C_9H_{21}N_2O_4^+$), 201.1 (100, $C_8H_{13}N_2O_4^+$), 189.2 (8, $C_8H_{17}N_2O_3^+$), 157.1 (8, $C_7H_{13}N_2O_2^+$), 57.3 (76, $C_4H_9^+$), 56.3 (39, $C_4H_8^+$).

25/26: TLC: R_f 0.30 (hexane/AcOEt/acetone 1:10:1, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.21–1.35 (*m*, CH_3(3.1), CH_3(3.3)); 1.39 (*s*, *t*-Bu); 2.90, 3.09 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.67 (*s*, CH_3O, further signals of rotamers); 3.76–4.62 (*m*, 2 H–C(2.2), 4.65 (*m*, H–C(2.1)); 5.18 (*m*, H–C(2.3)); 5.44 (*m*, H–N(2.1)). ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.17 (*d*, J = 7, CH_3(3.1 or 3.3)); 1.35 (*d*, J = 9, CH_3(3.1 or 3.3)); 1.40

(*s*, *t*-Bu); 2.85, 2.93 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 3.64 (*s*, CH_3O); 4.18 (*s*, 2 H–C(2.2)); 4.28–4.80 (*m*, H–C(2.1), H–C(2.3)); 5.85 (br. *m*, H–N(2.1)); at r.t. 2*s* at 3.64 and 3.69 (CH_3O). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.43 (CH_3(3.3)); 18.94 (CH_3(3.1)); 28.38 ($(CH_3)_3C$); 30.66 (CH_3–N(2.3)); 36.25 (CH_3–N(2.2)); 46.38 (CH(2.1)); 49.61 (CH_2(2.2)); 52.16 (CH(2.3)); 52.31 (CH_3O); 79.49 ($(CH_3)_3C$); 155.11 (*t*-BuO*C*O); 167.94, 172.08 (C(1.1), C(1.2)); 173.46 (C(1.3)). FAB-MS: 360.3 (39, $[M+1]^+$, $C_{16}H_{30}N_3O_6^+$), 304.3 (7, $C_{12}H_{22}N_3O_6^+$), 260.3 (19, $C_{11}H_{22}N_3O_4^+$), 243.2 (7, $C_{11}H_{19}N_2O_4^+$), 215.2 (8, $C_9H_{21}N_2O_4^+$), 201.2 (18, $C_9H_{19}N_3O_2^+$), 187.2 (77, $C_7H_{11}N_2O_4^+$), 143.2 (28, $C_6H_{11}N_2O_2^+$), 118.1 (57, $C_5H_{12}NO_2^+$), 54.3 (100, $C_4H_6^+$).

27. TLC: R_f 0.47 (hexane/AcOEt/acetone 1:10:1, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.16–1.43 (*m*, CH_3(3.1), CH_3(3.2), CH_3(3.3)); 1.39 (*s*, *t*-Bu); 2.80, 2.92 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.67, 3.69 (2*s*, CH_3O, rotamers); 4.61 (*m*, H–C(2.1)); 5.17, 5.49 (2*m*, H–C(2.2), H–C(2.3)); 5.35 (*m*, H–N(2.1)). ^{1}H-NMR (80 MHz, 150°, (D_6)DMSO): 1.16–1.43 (*m*, CH_3(3.1), CH_3(3.2), CH_3(3.3)); 1.38 (*s*, *t*-Bu); 2.84, 2.90 (CH_3–N(2.2), CH_3–N(2.3), H_2O); 3.63 (*s*, CH_3O); 4.3–5.4 (*m*, 3 H, H–C(2.1), H–C(2.2), H–C(2.3)); 6.00 (br. *m*, H–N(2.1)); at r.t. 2*s* at 3.61 and 3.64 (CH_3O). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.06, 14.16 (CH_3(3.2), CH_3(3.3)); 19.02 (CH_3(3.1)); 28.37 ($(CH_3)_3C$); 29.49–30.76 (CH_3–N(2.2), CH_3–N(2.3), rotamers); 46.79 (CH(2.1)); 49.80 (CH_2(2.2)); 52.24 (CH_3O); 52.30 (CH(2.3)); 79.63 ($(CH_3)_3C$); 155.10 (*t*-BuO*C*O); 170.54–172.81 (C(1.1), C(1.2), C(1.3)). FAB-MS: 374.3 (6, $[M+23]^+$, $C_{17}H_{32}N_3O_6^+$), 257.2 (27, $C_{12}H_{21}N_2O_4^+$), 215.2 (22, $C_9H_{21}N_2O_4^+$), 201.2 (63, $C_8H_{13}N_2O_4^+$), 118.0 (13, $C_5H_{12}NO_2^+$), 57.4 (100, $C_4H_8^+$).

Boc-Ala-Me-DL-*Phe-Sar-OMe* (**28**/**29**), *Boc-Ala-Sar-Me*-DL-*Phe-OMe* (**10c**/**30**). With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at 0°: A soln. of **6b** (459 mg, 1.38 mmol) and LiCl (360 mg, 8.49 mmol) in THF (30 ml) was cooled to −78°. After the addition of LDA (4.38 mmol) and 2 h of stirring, DMPU (3.0 ml), BuLi (3.1 ml, 4.38 mmol) and $PhCH_2Br$ (1.0 ml, 8.41 mmol) were added. Then, the temp. was allowed to rise to 0° over 3 h. After further 4 h of stirring at 0° and usual workup, 1.58 g of crude product were isolated. Esterification of 1.28 g and purification by FC (hexane/AcOEt 1:2; after elution of **28**, AcOEt) gave 30 mg (6%) of **29**, 49 mg (10%) of **28**, 38 mg (8%) of **10c**/**30**, and 2 mg (0.5%) of esterified starting material **6c**.

With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at −26°: To **6b** (446 mg, 1.35 mmol) and LiCl (383 mg, 9.04 mmol) in THF (30 ml), LDA (4.2 mmol) was slowly added, according to *Exper. 2*. After 2 h, DMPU (3.0 ml), BuLi (3.0 ml, 4.2 mmol), and $PhCH_2Br$ (1.0 ml, 8.41 mmol) were slowly added. After stirring for 2 h at −78°, the temp. was warmed to −26°, continuing stirring for 22 h. The reaction was stopped with 8 ml of 1N H_2SO_4, the mixture neutralized with 1N NH_3 and the solvent evaporated. The residue was taken up in CH_2Cl_2, washed with 1N H_2SO_4 and extracted twice with sat. $NaHCO_3$ soln. The combined basic phases were acidified with 1N H_2SO_4 to pH 2 and then extracted twice with CH_2Cl_2. After drying ($MgSO_4$) and evaporation, 942 mg of crude product was obtained, still containing DMPU according to ^{1}H-NMR. Esterification of 848 mg of the crude product and usual extraction with Et_2O gave only 313 mg of crude ester. Therefore, the aq. phase was extracted 3 × with AcOEt, resulting in additional 58 mg (14%) of esterified starting material **6c** containing DMPU. FC (silica gel, hexane/AcOEt 1:2) gave 45 mg (9%) of **29**, 107 mg (20%) of **28**, and 65 mg (12%) of **30**/**10c**.

28. TLC: R_f 0.37 (hexane/AcOEt 1:2, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.15, 1.28 (2*d*, J = 7,7, CH_3(3.1), rotamers); 1.37, 1.41 (2*s*, *t*-Bu, rotamers); 2.95, 2.98, 3.04 (3*s*, CH_3–N(2.2), CH_3–N(2.3), rotamers); 2.85 (*m*, H–C(3.2)); 3.28 (*m*, H–C(3.2)); 3.70 (*s*, CH_3O, further *s* of rotamers); 3.85–4.5 (*m*, 2H–C(2.3)); 4.58 (*m*, H–C(2.1)); 4.9, 5.24 (2*d*, J = 9, H–N(2.1)); 5.70 (*t*, J = 6, H–C(2.2)). ^{1}H-NMR (80 MHz, 150°, (D_6)DMSO): 1.17 (*d*, J = 6, CH_3(3.1)); 1.44 (*s*, *t*-Bu); 2.93, 2.98 (2*s*, CH_3–N(2.2), CH_3–N(2.3)); 2.75–3.3 (*m*, 2H–C(3.2)); 3.67 (*s*, CH_3O); 4.05–4.50 (*m*, H–C(2.1), 2H–C(2.3)); 5.55 (*t*, J = 7, H–C(2.2)); 6.00 (*m*, H–N(2.1)); 7.22 (*s*, 5 H, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.96 (CH_3(3.1)); 28.37 ($(CH_3)_3C$); 30.47 (CH_3–N(2.3)); 35.00 (CH_2(3.2)); 36.00 (CH_3–N(2.2)); 46.62 (CH(2.1)); 49.75 (CH_2(2.3)); 52.11 (CH_3O); 54.43 (CH(2.2)); 79.52 ($(CH_3)_3C$); 126.57–129.48 (5 CH, Ph); 137.13 (1 C, Ph); 154.99 (*t*-BuO*C*O); 169.30–172.70 (C(1.1) C(1.2), C(1.3)). FAB-MS: 436.2 (*s*, $[M+1]^+$, $C_{22}H_{34}N_3O_6^+$), 333.2 (26, $C_{18}H_{25}N_2O_4^+$), 277.2 (52, $C_{14}H_{17}N_2O_4^+$), 90.8 (8, $C_7H_7^+$), 87.7 (9), 56.4 (43, $C_4H_8^+$).

29. TLC: R_f 0.45 (hexane/AcOEt 1:2, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.68, 0.78 (2*d*, J = 7, 7, CH_3(3.1), rotamers); 1.37 (*s*, *t*-Bu); 2.89, 2.96, 2.98 (3*s*, CH_3–N(2.2), CH_3–N(2.3), rotamers); 3.05 (*m*, 2 H–C(3.2)); 3.73 (*s*, CH_3O, further *s* of rotamers); 3.87–4.48 (*m*, H–C(2.1), 2 H–C(2.3)); 5.20 (*m*, H–N(2.1)); 5.78 (*m*, H–C(2.2)); 7.22 (*m*, Ph). ^{1}H-NMR (80 MHz, 150°, (D^6)DMSO): 0.90 (*d*, J = 7, CH_3(3.1)); 1.37 (*s*, *t*-Bu); 2.93 (*s*, CH_3–N(2.2), CH_3–N(2.3)); 3.0 (*m*, 2 H–C(3.2)); 3.64 (*s*, CH_3O); 4.08 (*d*, J = 7, 2 H–C(2.3)); 4.35 (*m*, H–C(2.1)); 5.50–5.65 (*m*, H–C(2.2)); 5.8–6.2 (H–N(2.1)); 7.18 (*s*, 5 H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.58, 19.00 (CH_3(3.1)); 28.30 ($(CH_3)_3C$); 30.17 (CH_3–N(2.3)); 35.12 (CH_2(3.2)); 36.39 (CH_3–N(2.2)); 36.54 (CH(2.1)); 50.17, 50.95 (CH_2(2.3)); 52.15 (CH_3O); 53.34, 53.83 (CH(2.2)); 79.53 ($(CH_3)_3C$); 126.68, 128.26, 129.52 (5 CH, Ph); 136.70 (1 C, Ph); 154.93, 155.31 (*t*-BuO*C*O); 169.33–172.97 (C(1.1), C(1.2), C(1.3)). FAB-MS: 436.2 (9, $[M+1]^+$, $C_{22}H_{34}N_3O_6^+$), 333.2 (23, $C_{18}H_{25}N_2O_4^+$), 277.2 (57, $C_{14}H_{17}N_2O_4^+$), 233.2 (6, $C_{13}H_{17}N_2O_2^+$), 90.8 (7, $C_7H_7^+$), 87.7 (11), 56.4 (46, $C_4H_8^+$).

10c/30. TLC: R_f 0.18 (hexane/AcOEt 1:2, ninhydrin). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.28 (*m*, CH_3(3.1)); 1.40 (*s*, *t*-Bu); 2.79, 2.87 (2*s*, CH_3–N(2.2), CH_3–N(2.3), further signals of rotamers); 3.00 (*m*, H–C(3.3)); 3.32 (*m*, H–C(3.3)); 2.71 (*s*, CH_3O, further signals of rotamers); 3.8–4.6 (*m*, 2 H–C(2.2)); 4.57 (*m*, H–C(2.1)); 5.25 (*m*, H–C(2.3)); 5.43 (*t*, *J* = 7, H–N(2.1)); 7.19 (*m*, 5 H, Ph). ^{1}H-NMR (80 MHz, 150°, (D_6)DMSO): 1.17, 1.19 (2*d*, *J* = 7, 7, CH_3(3.1), possibly diastereosiomers); 1.43 (*s*, *t*-Bu); 2.79, 2.83 (CH_3–N(2.2), CH_3–N(2.3), H_2O); 3.13, 3.23 (2*d*, *J* = 9, 5, 2 H–C(3.3)); 3.70 (*s*, CH_3O); 4.09 (br. *s*, 2 H–C(2.2)); 4.35 (*d*, *J* = 7, H–C(2.1)); 5.03 (2*d*, *J* = 5, 9, H–C(2.3)); 6.0 (br. *s*, H–N(2.1)); 7.26 (*s*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.94 (CH_3(3.1)); 28.39 ((CH_3)$_3$C); 32.11 (CH_3–N(2.3)); 34.70 (CH_2(3.3)); 35.67 (CH_3–N(2.2)); 46.35 (CH(2.1)); 49.17 (CH_2(2.2)); 52.35 (CH_3O); 58.56, 61.01 (CH(2.3)); 79.46 ((CH_3)$_3$*C*); 126.83–129.15 (5 CH, Ph); 136.86 (1 C, Ph); 155.12 (*t*-BuO*C*O); 168.16–173.26 (C(1.1), C(1.2), C(1.3)). FAB-MS: 568.2 (7, $[M + 133]^+$, $C_{22}H_{33}N_3O_6Cs$), 458.2 (5, $[M + 23]^+$, $C_{22}H_{33}N_3O_6Na^+$), 436.1 (33, $[M + 1]^+$, $C_{22}H_{34}N_3O_6^+$), 336.1 (14, $C_{17}H_{26}N_3O_4^+$), 333.2 (30, $C_{17}H_{23}N_3O_4^+$), 291.1 (8, $C_{15}H_{19}N_2O_4^+$), 277.2 (57, $C_{13}H_{15}N_3O_4^+$), 265.1 (36, $C_{14}H_{21}N_2O_3^+$), 243.3 (7, $C_{11}H_{19}N_2O_4^+$), 194.2 (46, $C_{11}H_{16}NO_2^+$), 187.2 (53, $C_7H_{11}N_2O_4^+$), 143.1 (17, $C_6H_{11}N_2O_2^+$), 90.7 (17, $C_7H_7^+$), 87.7 (22), 56.4 (100, $C_4H_8^+$).

*Boc-Ala-Me-*DL-*Abu-MeLeu-OCH$_3$* (**31**). With deprotonation of (i-Pr)$_2$NH, with BuLi, addition of DMPU; alkylation at –78°: To a soln. of **7b** (495 mg, 1.3 mmol) and LiCl (336 mg, 8 mmol) in THF (20 ml), LDA (4.2 mmol) was slowly added at –78°. After 1.5 h BuLi (2.8 ml, 4.2 mmol, 1.5 h), DMPU (2 ml) and EtI (0.67 ml, 8.3 mmol) was added. After 19 h at –78° and workup as usual, 759 mg of crude product was isolated. Esterification and FC (hexane/AcOEt/acetone 10:10:1) gave 63 mg (0.15 mmol, 11%) **31**. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.83–1.03 (*m*, CH_3(5.3), CH_3(5′.3), CH_3(4.2)); 1.35 (*d*, *J* = 7, CH_3(3.1)); 1.43 (*s*, *t*-Bu); 1.66–2.06 (*m*, 2 H–C(3.2), 2 H–C(3.3), H–C(4.3)); 2.83 (*s*, CH_3–N(2.3)); 2.96 (*s*, CH_3–N(2.2)); 3.66 (*s*, CH_3O); 4.40–4.73 (*m*, H–C(2.1)); 5.10–5.46 (*m*, H–C(2.2), H–C(2.3)).

*Boc-Ala-Me-*DL-*Ape(4-en)-MeLeu-OMe* (**32/33**). With deprotonation of (i-Pr)$_2$NH with BuLi, addition of DMPU; alkylation at –78°. To a soln. of **7b** (498 mg, 1.285 mmol) and LiCl (307 mg, 7.24 mmol) in THF (20 ml), LDA (4.2 mmol) was slowly added at –78°. After 2 h, BuLi (3.0 ml, 4.2 mmol) DMPU (3.0 ml), and allyl bromide (0.8 ml, 9.46 mmol) was slowly added (→red soln., colour disappeared slowly after a few min). After 21 h stirring at –78° and workup as usual, 680 mg of crude product was isolated. Esterification of 510 mg and FC (hexane/AcOEt/acetone 10:10:1) provided 133 mg (32%) of **32/33**, 240 mg (48%) of esterified starting material, and 73 mg of unknown by-product.

With deprotonation of (i-Pr)$_2$NH with BuLi, addition of HMPT; alkylation at –78°: From **7b** (496 mg, 1.3 mmol), THF (20 ml), LDA (4.2 mmol), HMPT (2 ml; 2 h stirring), and allyl bromide (1 ml, 1.43 g, 11.8 mmol). Stirring overnight and workup, yielded 173 mg (31%) of crude product. After purification, the spectra were identical with those of the products of the reaction with DMPU as cosolvent.

32/33: TLC: R_f 0.52 (hexane/AcOEt/acetone 10:10:1, UV). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*d*, *J* = 6, CH_3(5.3)); 0.95 (*d*, *J* = 7, CH_3(5′.3)); 1.28 (*d*, *J* = 7, CH_3(3.1)); 1.42 (*s*, *t*-Bu); 1.45–1.54 (*m*, H–C(4.3)); 1.63–1.79 (*m*, 2 H–C(3.3)); 2.48–2.63 (*m*, 2 H–C(3.2)); 2.81 (*s*, CH_3–N(2.3)); 2.97 (*s*, CH_3–N(2.2)); further signals at 2.92–3.17 of rotamers (CH_3–N(2.2), CH_3–N(2.3)); 3.70, 3.71, 3.75 (3*s*, CH_3O, rotamers); 4.60 (*m*, H–C(2.1)); 5.03 (br. *d*, long-range-coupling with 2 H–C(3.2), *J* (4.2, 5.2) = 10, H–C(5.2) *cis* to H–C(4.2)); 5.09 (*dd*, *J* (4.2, 5′.2) = 17, J_{gem} = 1, H–C(5′.2) *trans* to H–C(4.2)); 5.23–5.28 (2*d*, *J* = 5, 5, H–C(2.3)); 5.34 (*d*, *J* = 8, H–N(2.1)); 5.51–5.56 (2*d*, *J* = 6, 6, H–C(2.2)); 5.63–5.76 (*m*, H–C(4.2)). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.16 (CH_3(3.1)); 21.41 (CH_3(5.3)); 23.22 (CH_3(5′.3)); 25.04 (CH(4.3)); 28.32, 28.38 ((CH_3)$_3$C); 30.03 (CH_3–N(2.3)); 30.64 (CH_3–N(2.2)); 33.80 (CH_2(3.2)); 36.70 (CH_2(3.3)); 46.60 (CH(2.1)); 52.22 (CH_3O); 52.94 (CH(2.2)); 54.90 (CH(2.3)); 79.58 ((CH_3)$_3$*C*); 118.03 (CH_2(5.2)); 133.78 (CH(4.2)); 155.21 (*t*-BuO*C*O); 170.15 (C(1.1)); 171.89 (C(1.2)); 173.17 (C(1.3)).

*Boc-Ala-Me-*DL-*Ape-MeLeu-OMe* (**34/35**). To 31 mg (0.07 mmol) of **32/33** in AcOEt (5 ml), 10% Pd/C (30 mg) was added. The mixture was stirred for 5 h under H_2 at r.t. Filtration through talc and evaporation gave 29 mg (86%) of **34/35**. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*d*, *J* = 6.5, CH_3(5.3)); 0.94 (*d*, *J* = 6.5, CH_3(5′.3)); 0.88–0.99 (*m*, CH_3(5.2)); 1.15–1.36 (*m*, H–C(4.3), 2 H–C(4.2)); 1.32 (*d*, *J* = 7, CH_3(3.1)); 1.42 (*s*, *t*-Bu); 1.59–1.84 (*m*, 2 H–C(3.3), 2 H–C(3.2)); 2.83 (*s*, CH_3–N(2.3)); 2.98 (*s*, CH_3–N(2.2)); 3.71 (*s*, CH_3O); further signals of rotamers at 3.00–4.25 (CH_3–N(2.2), CH_3–N(2.3), H–C(2.1), H–C(2.2), H–C(2.3), CH_3O); 4.61–4.65 (*m*, H–C(2.1)); 5.22–5.28 (*dd*, *J* = 5, H–C(2.2)); 5.38–4.45 (*m*, H–N(2.1), H–C(2.3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.84 (CH_3(5.2)); 18.56 (CH_3(3.1)); 18.96 (CH_2(4.2)); 21.61 (CH_3(5.3)); 23.11 (CH_3(5′.3)); 25.17 (CH(4.3)); 28.44 ((CH_3)$_3$C); 30.09 (CH_3–N(2.3)); 30.96 (CH_3–N(2.2)); 31.40 (CH_2(3.2)); 37.16 (CH_2(3.3)); 46.87 (CH(2.1)); 53.34 (CH(2.3)); 55.29 (CH(2.2)); 79.62 ((CH_3)$_3$*C*); 155.21 (*t*-BuO*C*O); 170.78 (C(1.1)); 171.87 (C(1.2)); 173.17 (C(1.3)).

*Boc-Ala-Me-*DL-*Phe-MeLeu-OMe* (**36/37**). According to *Exper. 2*, with **7b** (506 mg, 1.3 mmol), LiCl (389 mg, 9 mmol), DMPU (2 ml), and $PhCH_2Br$ (1 ml, 1.4 g, 8.2 mmol). On addition of $PhCH_2Br$, the soln. became blue for 30 to 45 min. After stirring for 18 h at –70°, the soln. was clear and yellow with a viscous deposit which became less

viscous upon warming up to r.t. The reaction was stopped by adding 1 ml of pH 7 buffer. After evaporation, the product was taken up in Et_2O and washed with pH 7 buffer. Drying ($MgSO_4$) and evaporating gave 206 mg (33%) of crude product which was dissolved in Et_2O and washed with sat. $NaHCO_3$ soln. The aq. phase was acidified with 1N H_2SO_4 to pH 2–3 and extracted once again with Et_2O. Drying ($MgSO_4$) of the org. phase, evaporation, and recystallization from Et_2O/hexane provided 112 mg (20%) of colourless cystals. ^{13}C- and ^1H-NMR: **36/37** > 20:1. ^1H-NMR (300 MHz, $CDCl_3$): 0.85 (*d*, *J* = 6.5, CH_3(5.3)); 0.89 (*d*, *J* = 6.6, CH_3(5'.3)); 0.85–0.98 (br. *m*, CH_3(3.1)); 1.38 (*s*, *t*-Bu); 1.26–1.53 (*m*, H–C(4.3)); 1.59–1.85 (*m*, 2 H–C(3.3)); 2.80 (*s*, CH_3N); 2.98 (*s*, CH_3N); 3.16–3.23 (*m*, 2 H–C(3.2)); 4.48–4.50 (*m*, H–C(2.1)); 5.21–5.26 (*dd*, *J* = 5, H–C(2.2)); 5.30 (br. *d*, *J* = 8, H–N(2.1)); 5.77 (*t*, *J* = 7.7, H–C(2.3)); 7.15–7.25 (*m*, Ph). ^1H-NMR (300 MHz, 100°, (D_6)DMSO): 0.82 (*d*, *J* = 6.5, CH_3(5.3)); 0.86 (*d*, *J* = 6.6, CH_3(5'.3)); 0.93 (br. *s*, CH_3(3.1)); 1.37 (*s*, *t*-Bu, H–C(4.3)); 1.58–1.66 (*m*, 2 H–C(3.3)); 2.81 (*s*, CH_3N); 2.96 (*s*, CH_3N); 3.11–3.13 (*m*, 2 H–C(3.2)); 4.49 (*m*, H–C(2.1)); 4.93 (br. *s*, H–C(2.2)); 5.63 (br. *s*, H–N(2.1)); 6.21 (br., H–C(2.3)); 7.13–7.25 (*m*, 5 H, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.80 (CH_3(3.1)); 21.43 (CH_3(5.3)); 23.13 (CH_3(5'.3)); 24.86 (CH(3.3)); 28.33 ((CH_3)$_3$C); 30.31 (CH_3–N(2.3)); 30.87 (CH_3–N(2.2)); 35.46 (CH_2(4.3)); 36.64 (CH_2(3.2)); 46.71 (CH(2.1)); 54.61 (CH(2.3)); 55.19 (CH(2.2)); 79.97 ((CH_3)$_3C$); 126.64, 128.24, 129.53, 136.68 (5 CH, 1 C, Ph); 155.51 (*t*-BuO*C*O); 170.44 (C(1.1)); 172.96 (C(1.2)); 173.52 (C(1.3)). Anal. calc. for $C_{25}H_{39}N_3O_6$ (477.60): C 62.87, H 8.23, N 8.80; found: C 63.12, H 8.48, N 8.61.

Boc-Ala-DL-*Thr-MeLeu-OMe* (**38**). According to *Exper. 2*, with **7b** (415 mg, 1.07 mmol) LiCl (282 mg, 6.65 mmol), THF (20 ml), and acetaldehyde (0.39 ml, 7 mmol). After 150 min of stirring at −78°, the reaction was stopped by addition of 1 ml of pH 7 buffer. After warming up to r.t., the mixture was taken up in AcOEt and washed with 1N H_2SO_4. Drying ($MgSO_4$) of the org. layer and evaporation gave 560 mg of crude product. After esterification with diazomethane, the product was purified by chromatography (hexane/AcOEt/acetone 10:10:1): 185 mg (40%) of **38**. ^1H-NMR (200 MHz, $CDCl_3$): 0.90 (*d*, *J* = 5, CH_3(5.3)); 0.93 (*d*, *J* = 5, CH_3(5'.3)); 1.16 (*m*, CH_3(4.2)); 1.29 (*m*, CH_3(3.1)); 1.40 (*s*, *t*-Bu, H–C(4.3)); 1.62–1.81 (*m*, 2 H–C(3.3)); 2.73, 2.81, 2.82 (3*s*, CH_3–N(2.3), rotamers); 2.98, 2.99, 3.02, 3.11 (4*s*, CH_3–N(2.2), rotamers); 3.65, 3.70, 3.71 (3*s*, CH_3O, rotamers); 3.42 (br. *s*, OH); 3.50 (*d*, *J* = 6, H–N(2.1)); 4.06–4.35 (*m*, H–C(2.1)); 4.50–4.71 (*m*, H–C(2.2)); 5.01–5.36 (*m*, H–C(3.2), H–C(2.3)).

Boc-Ala-Me-DL-*Ser(3-*t*-Bu)-MeLeu-OMe* (**39**). To a soln. of **7b** (500 mg, 1.3 mmol) and LiCl (336 mg, 8 mmol) in THF (20 ml) was added, according to *Exper. 2*, pivalaldehyde (0.9 ml, 8.3 mmol). After 70 min of stirring at −78°, 1 ml of pH 7 buffer was added and the soln. warmed to r.t. The org. phase was washed with 1N H_2SO_4 and dried ($MgSO_4$). The resulting crude product (990 mg) was esterified with diazomethane. Purification by chromatography (hexane/AcOEt/acetone 10:10:1) gave 261 mg (42%) of **39**. ^1H-NMR (90 MHz, $CDCl_3$): 0.97 (*m*, CH_3(5.3), C(4.3), CH_3(5'.3), *t*-Bu-C(2.3)); 1.32 (*m*, CH_3(3.1), H–C(4.3)); 1.45 (*s*, *t*-BuO); 1.73 (*m*, 2 H–C(3.3)); 2.82, 2.91 (2 *s*, CH_3–N(2.3), rotamers); 3.16, 3.22 (2 *s*, CH_3–N(2.2), rotamers); 3.71 (*s*, CH_3O); 4.00–5.70 (*m*, H–C(2.1), H–C(2.2), H–C(2.3), H–C(3.2), OH, H–N(2.1)).

Boc-Ala-Me-DL-*Ser(3-Ph)-MeLeu-OMe* (**40/41/42/43**). According to *Exper. 2*, with LiCl (309 mg, 7.29 mmol), **7b** (533 mg, 1.38 mmol), and LDA (4.4 mmol). After 2 h, BuLi (3.2 ml) and benzaldehyde (0.8 ml, 8.0 mmol) were added, stirred for 135 min at −78° and worked up as usual: 1.430 g of crude product. Esterification of 1.199 g with diazomethane and FC (CH_2Cl_2/Et_2O 8.5:1.5) gave benzaldehyde (R_f 0.78), 55 mg of benzyl alcohol (R_f 0.44), and 10 mg of different impurities (R_f 0.39–0.31), separated from 273 mg of **40/41** (R_f 0.27) and 220 mg of **42/43** (R_f 0.18). The mixture **40/41** was separated by further FC, (hexane/AcOEt 1:1) into **40** (92 mg, 16%; R_f 0.35) and **41** (158 mg, 27%; R_f 0.28). Further FC (hexane/AcOEt 1:1) of **42/43** did not lead to separation but resulted in 171 mg (29%) of **42/43**.

40. TLC: R_f 0.27 (CH_2Cl_2/Et_2O 8.5:1.5, anisaldehyde); R_f 0.35 (hexane/AcOEt 1:1, anisaldehyde), R_f 0.45 (hexane/AcOEt/acetone 10:10:1.5, anisaldehyde). ^1H-NMR (300 MHz, $CDCl_3$): 0.70 (*d*, *J* = 7, CH_3(3.1)); 0.88 (*d*, *J* = 6, CH_3(5.3)); 0.93 (*d*, *J* = 7, CH_3(5'.3)); 1.37 (*s*, *t*-Bu); 1.39 (*m*, H–C(4.3)); 1.69–1.77 (*m*, 2 H–C(3.3)); 2.77 (*s*, CH_3–N(2.3)); 3.04 (*s*, CH_3–N(2.2)); 3.72 (*s*, CH_3O); 3.78 (*d*, *J* = 5, OH); 4.38 (*m*, H–C(2.1)); 5.07–5.14 (*m*, H–C(2.2), H–C(3.2)); 5.31 (2*d*, *J* = 5, 5, H–C(2.3)); 5.63 (*d*, *J* = 8, H–N(2.1)); 7.25–7.41 (*m*, Ph); D_2O exchange: *d* at 3.78 disappeared, *m* at 5.07–5.14 changed. ^{13}C-NMR (100 MHz, $CDCl_3$): 17.19 (CH_3(3.1)); 21.35 (CH_3(5.3)); 23.20 (CH_3(5'.3)); 24.74 (CH(4.3)); 28.24 ((CH_3)$_3$C); 30.65 (CH_3–N(2.3)); 31.52 (CH_3–N(2.2)); 36.53 (CH_2(3.3)); 46.30 (CH(2.1)); 52.33 (CH_3O); 54.90 (CH(2.3)); 58.31 (CH(2.2)); 73.60 (CH(3.2)); 79.55 ((CH_3)$_3C$); 127.37, 128.15, 128.24 (5 CH, Ph); 139.96 (1 C, Ph); 155.28 (*t*-BuO*C*O); 170.85 (C(1.1)); 171.57 (C(1.2)); 172.77 (C(1.3)). FAB-MS: 508.3 (19, $[M+1]^+$, $C_{26}H_{42}N_3O_7^+$), 490.3 (15, $C_{26}H_{40}N_3O_6^+$), 434.2 (21, $C_{22}H_{32}N_3O_6^+$), 401.2 (10, $C_{19}H_{35}N_3O_6^+$), 349.2 (12, $C_{18}H_{25}N_2O_5^+$), 337.3 (8, $C_{18}H_{29}N_2O_4^+$), 293.2 (11, $C_{14}H_{17}N_2O_5^+$), 243.3 ($C_{11}H_{19}N_2O_4^+$), 229.3 (19, $C_{11}H_{21}N_2O_3^+$), 187.2 (42, $C_7H_{11}N_2O_4^+$), 160.2 (16, $C_8H_{18}NO_2^+$), 55.4 (100, $C_4H_8^+$).

41. TLC: R_f 0.27 (CH_2Cl_2/Et_2O 8.5–1.5, anisaldehyde); R_f 0.28 (hexane/AcOEt 1:1, anisaldehyde); R_f 0.38 (hexane/AcOEt/acetane 10:110:1.5, anisaldehyde). ^1H-NMR (200 MHz, $CDCl_3$): 0.89–1.14 (*m*, CH_3(5.3),

CH_3(3.1)); 1.40 (*s*, *t*-Bu); 1.41 (*m*, H–C(4.3)); 1.64–1.77 (*m*, 2 H–C(3.3)); 2.78, 2.81 (2*s*, CH_3–N(2.3), rotamers); 2.94, 2.95 (2 *s*, CH_3–N(2.2), rotamers); 3.61, 3.66 (2*s*, CH_3O); 4.06–4.14 (*m*, OH); 4.27–4.57 (*m*, H–C(2.1), H–C(2.3)); 4.86–5.17 (*m*, H–C(2.2), H–C(3.2)); 5.37, 5.49 (2 *d*, J = 8, 8, H–N(2.1), rotamers); 7.18–7.40 (*m*, 5 H, Ph); D_2O exchange: signal at 4.06–4.14 disappeared, signal at 4.86–5.17 changed. ^{1}H-NMR (80 MHz, 150°, (D_6) DMSO): 0.85–1.10 (*m*, CH_3(3.1), CH_3(5.3), CH_3(5'.3)): 1.25–1.40 (*s* and *m*, *t*-Bu, H–C(4.3)); 1.55–1.85 (*m*, 2 H–C(3.3)); 2.85, 2.96, (2 CH_3N, H_2O); 3.64 (*s*, CH_3O); 4.10–5.6 (*m*, H–C(2.1), H–C((2.2), H–C(3.2), H–C(2.3), NH, OH); 7.12–7.38 (*m*, Ph); at r.t., 3.56, 3.73 (2 *s*, CH_3O). ^{13}C-NMR (50 MHz, $CDCl_3$): 17.74 (CH_3(3.1)); 20.24 (CH_3(5.3)); 22.30 (CH_3(5'.3)); 24.06 (CH(4.3)); 27.40 ((CH_3)$_3$C); 30.94, 31.49 (2 CH_3N); 36.16, 37.56 (CH_2(3.3)); 45.28 (CH(2.1)); 51.47, 54.73 (CH_3O); 57.02 (CH(2.3)); 58.43 (CH(2.2)); 72.42, 72.82 (CH(3.2)); 78.79 ((CH_3)$_3C$); 126.22, 126.71, 127.45 (5 CH, Ph); 138.69 (1 C, Ph); 154.13 (*t*-BuO*C*O); 170.23–171.81 (C(1.1), C(1.2), C(1.3)). FAB-MS: 508.4 (37, $[M+1]^+$, $C_{26}H_{42}N_3O_7^+$), 490.2 (8, $C_{26}H_{40}N_3O_6^+$), 434.1 (14, $C_{22}H_{32}N_3O_6^+$), 401.2 (14, $C_{19}H_{35}N_3O_6^+$), 349.1 (83, $C_{18}H_{25}N_2O_5^+$), 337.1 (11, $C_{18}H_{29}N_2O_4^+$), 293.1 (68, $C_{14}H_{17}N_2O_5^+$), 243.1 (19, $C_{11}H_{19}N_2O_4^+$), 229.1 (32, $C_{11}H_{21}N_2O_3^+$), 187.1 (100, $C_7H_{11}N_2O_2^+$), 160.2 (53, $C_8H_{18}NO_2^+$), 56.3 (55, $C_4H_8^+$).

42/43. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.83–1.05 (*m*, CH_3(5.3), CH_3(5'.3)); 1.14–1.23 (*m*, CH_3(3.1)); 1.35, 1.42 (2 *s*, *t*-Bu, H–C(4.3)); 1.60–1.87 (*m*, 2 H–C(3.3)); 2.71, 3.18, 3.20 (3 *s*, 2 CH_3N, further signals of rotamers); 3.58, 3.61, 3.68 (3 *s*, CH_3O); 4.10, 4.5 (2 br. *d*, J = 5, OH); 4.40–4.62 (*m*, H–C(2.1)); 4.88–5.29 (*m*, 3 H, H–C(2.2), H–C(3.2), H–C(2.3)); 5.54–5.68 (*m*, NH); 7.20–7.40 (*m*, Ph); D_2O exchange: signals at 4.1 and 4.5 disappeared. ^{1}H-NMR (80 MHz, 150°, (D_6)DMSO): 0.67–0.85 (*m*, CH_3(5.3), CH_3(5'.3)); 1.20 (*d*, J = 7, CH_3(3.1)); 1.23–1.75 (*s*, *m*, *t*-Bu, H–C(4.3), 2 H–C(3.3)); 2.67–3.14 (some *s*, 2 CH_3N, H_2O); 4.02, 4.06 (2*s*, CH_3O); 4.4–5.65 (*m*, H–C(2.1), H–C(2.2), H–C(3.2), H–C(2.3), OH); 6.05 (br. *d*, J = 6, NH); 7.15–7.30 (*m*, Ph). ^{13}C-NMR (50 MHz, $CDCl_3$): 17.88, 18.50 (CH_3(3.1)); 21.31 (CH_3(5.3)); 23.23 (CH_3(5'.3)); 24.56, 24.80 (CH(4.3)); 28.30 ((CH_3)$_3$C); 30.87 (CH_3–N(2.3)); 31.75 (CH_3–N(2.3)); 36.60, 36.99 (CH_2(3.3)); 46.55 (CH(2.1)); 52.15, 52.40 (CH_3O); 54.78, 55.22 (CH(2.3)); 57.34, 57.89 (CH(2.2)); 72.62, 73.75 (CH(3.2)); 79.59, 79.87 ((CH_3)$_3C$); 127.08–128.39 (5 CH, Ph); 140.04 (1 C, Ph); 155.48, 155.65 (*t*-BuO*C*O); 170.30–174.21 (C(1.1), C(1.2), C(1.3)). FAB-MS: 508.2 (18, $[M+1]^+$, $C_{26}H_{42}N_3O_7^+$), 490.2 (14, $C_{26}H_{40}N_3O_6^+$), 434.1 (26, $C_{22}H_{32}N_3O_6^+$), 401.4 (4, $C_{19}H_{35}N_3O_6^+$), 349.1 (25, $C_8H_{25}N_2O_5^+$), 337.1 (19, $C_{18}H_{29}N_2O_4^+$), 293.0 (26, $C_{14}H_{17}N_2O_5^+$), 243.1 (9, $C_{11}H_{19}N_2O_4^+$), 229.1 (32, $C_{11}H_{21}N_2O_3^+$), 187.1 (55, $C_7H_{11}N_2O_4^+$), 160.3 (76, $C_8H_{18}NO_2^+$), 56.3 (100, $C_4H_8^+$).

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