37. *C*-Alkylation of Sarcosine Residues in Cyclic Tetrapeptides *via* Lithium Enolates

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The cyclic tetrapeptides cyclo(-Leu-Sar-Sar-Gly-), cyclo(-Val-Sar-Sar-Gly-), and cyclo(-MeLeu-Gly-D-Ala-Sar-) have been synthesized from the component amino acids (BOP-Cl coupling), using the pentafluorophenyl esters for the cyclization step (42, 13, and 30% yield, respectively). Multiple deprotonation (LDA in THF/LiBr/DMPU) and addition of highly reactive electrophiles (CF_3CO_2D, MeI, CH_2O, CH_2CHCH_2Br, $PhCH_2Br$) produce cyclic tetrapeptides with additional substituents introduced diastereoselectively (70 to > 98% ds) in yields ranging from 20 to 90%. The *C*-alkylated products are all derived from a sarcosine-enolate moiety adjacent to another *N*-methylamino acid. The structures of the resulting products are determined by NMR spectroscopy (DNOE and ROESY techniques) and by hydrolysis to the parent amino acids, suitable derivatization, and analysis by chromatography on a chiral GC column. It was shown in two cases that the overall yield of cyclization/alkylation to give a disubstituted cyclic tetrapeptide is higher than that of a synthesis of the same product from the corresponding amino-acid building blocks. Surprising temperature and salt effects on the yields and selectivities of the reactions of the cyclic tetrapeptide enolates are presented, and possible mechanistic interpretations are discussed.

1. Introduction. – Cyclic tetrapeptides have been isolated from microorganisms and fungi as cytotoxic or phytotoxic compounds (for examples, see *Scheme 1*). Typically, they contain nonproteinogenic amino acids such as amino acids with (*R*)-configuration, *N*-methylamino acids, or dehydroamino acids. In addition, they tend to have rigid conformations frequently containing *cis*-peptide bonds.

The synthesis of natural and unnatural cyclic tetrapeptides has been studied extensively [5–10][3]). The rate of cyclization of linear tetrapeptides depends on their conformation. Cyclization yields are frequently enhanced by the presence of glycine, (*R*)-amino acids, sarcosine, or cyclic amino acids[4]). Generally, ring closure becomes more difficult the greater the number of side chains on the peptide, and cyclization yields vary greatly depending on the amino-acid sequence of the linear precursor [11a–c] [12b]. It would, therefore, be advantageous to synthesize less highly substituted cyclic peptides and introduce the substituents after the cyclization step. This amounts to the modification of a given peptide rather than its synthesis from the corresponding components (*Scheme 2*).

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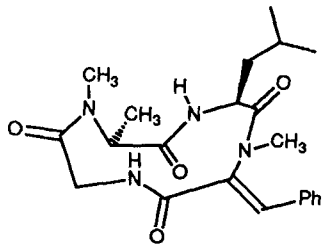
[2]) Part of the undergraduate senior research project of *S.L.G.*, under the auspices of the exchange program between Imperial College (London) and ETH-Zürich, 1991.

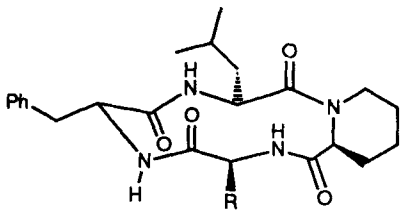
[3]) For reviews on the synthesis of small cyclic peptides, see [11].

[4]) Even the tripeptide Pro-Pro-Pro cyclizes readily [12a].

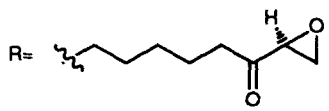
Scheme 1. *Four Representatives of Natural Cyclic Tetrapeptides*

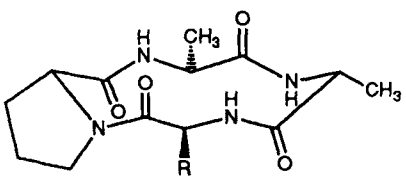


Tentoxin: cyclo(-Leu-Me(Z)ΔPhe-Gly-MeAla-) [1]

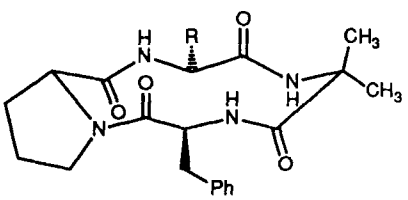


WF 3161: cyclo(-Aoe-D-Phe-Leu-Pip-) [2]



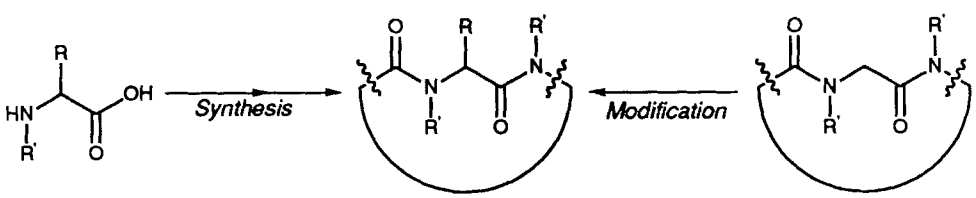


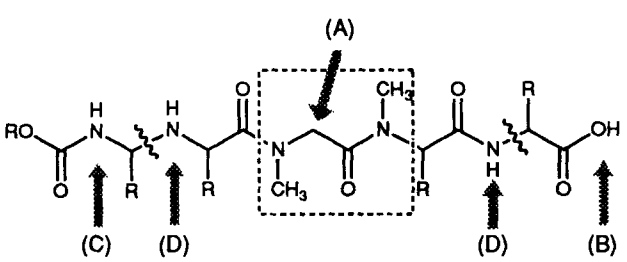
HC-Toxin: cyclo(-Aoe-D-Pro-Ala-D-Ala-) [3]



Chlamydocin: cyclo(-Aoe-Aib-Phe-D-Pro-) [4]

Scheme 2. *Two Principles for Incorporation of Side-Chain Substituents into Cyclic Peptides and Structural Requirements for Enolate Formation in a Peptide*





In previous work [13] [14], we have shown that enolates of peptides can be generated and *C*-alkylated under certain conditions: *a*) the peptide must contain a sarcosine unit with a second *N*-methylamino acid attached to it (see A, *Scheme 2*), *b*) the C-terminus must be a free carboxylic acid (B), the N-terminus carbamate protected (C), and *c*) the remaining amide N-atoms need to be unprotected (D).

Peptides fulfilling these conditions and containing up to seven amino-acid residues have been polylithiated by abstraction of the protons from the COOH and all the NH groups, as well as of a proton from the sarcosine CH_2 group. We believe that the deprotonations (type B, C, and D in *Scheme 2*) protect the neighboring stereogenic centers from being epimerized under the strongly basic reaction conditions [14]. Critical to the success of this procedure is the ability to solubilize both the peptide [15] and its polylithio derivative [13] [14] in an organic solvent such as THF by the addition of a Li salt.

At the outset of the present work, we had hoped that the conformational restrictions present in small cyclic peptides would result in a greater selectivity of the transformation outlined above (*Scheme 2*). We expected that, by analogy to the medium-ring carbocycles alkylated by *Still* and *Novak* [16], attack of the electrophile would occur only from the outside of the ring, resulting in *one* product.

2. Preparation, Structure, and Properties of the Cyclic Tetrapeptide Starting Materials. – For this study, we chose to prepare the cyclic tetrapeptides **1**–**3** bearing only one or two side chains. The component amino acids were assembled through the intermediates **4**–**11** (→**1**), **12**–**19** (→**2**), **20**–**27** (→**3**) as depicted in *Table 1*.

The peptides were constructed in the N to C direction starting with a (*tert*-butoxy)carbonyl(Boc)-protected amino acid, and using BOP-Cl as the coupling reagent [14] [17] [18]. The activation for the cyclization step was achieved with the pentafluorophenyl ester as generally recommended for small peptides by *Schmidt et al.* [9c] and *Sheh* and *Mokotoff* [19] (see *Scheme 3*). The cyclization yields for the formation of **1** and **3** may be considered good (30–40%), while **2** (*Scheme 3*) was obtained in only 13% yield.

The conformations of the cyclic tetrapeptides **1**–**3** as shown in *Scheme 3* were determined by difference nuclear *Overhauser* (DNOE) spectroscopy in (D_6)DMSO or $CDCl_3$. While compounds **1** and **3** had this very same conformation in all other solvents tested (D_2O, D_3COD, $CDCl_3$, and (D_8)THF), **2** displayed two conformations in $CDCl_3$. Very helpful in the NMR analysis were the measurements and compilation of literature data, reported by *Rayudu* [7][5]).

Generally, the NMR spectra, in contrast to those of the linear precursors, are pleasantly easy to interpret. Substituents on the tetrahedral centres occupy the pseudo-equatorial or outside position of the ring, and the diastereotopic methylene protons show large shift differences (up to 2.2 ppm), with the inside protons at lower field (for numbering and indices see formula **28a** in *Fig. 1* below). In agreement with previous findings [6], the conformers[6]) of cyclic tetrapeptides which we encountered in the present work appear to have rigid structures, at least on the NMR time scale. In most cases, the ring backbone adopts a 'zigzag', centrosymmetric *cis-trans-cis-trans* (*ctct*) arrangement [6a], with the C=O

[5]) This compilation includes work by *Dale* and *Titlestad* [6]; *Meyer et al.* [1b]; and *Rich et al.* [8].

[6]) For theoretical discussions of the energetics of cyclic tetrapeptide conformations, see [20].

Table 1. *Synthesis of the Linear Precursors of the Cyclic Peptides* **1–3**. Unless otherwise noted, the coupling agent was BOP-Cl (in CH_2Cl_2) and the deprotections were accomplished by catalytic hydrogenation (H_2/10% Pd/C in MeOH). The pentafluorophenyl(PFP)-active esters were prepared by reacting the peptide with pentafluorophenyl trifluoroacetate in pyridine.

a) cyclo(-Leu-Sar-Sar-Gly-) (**1**) Precursors

Product Number	Leu	Sar	Sar	Gly	Yield [%]
	Boc — OH H —	OBzl			
4	Boc —	OBzl			71
5	Boc —	OH H —	OBzl		97
6	Boc —		OBzl		94
7	Boc —		OH H —	OBzl	99
8	Boc —			OBzl	47
9	Boc —			OH	99
10	Boc —			OPFP	[a])
11	H —			OPFP	[a])

b) cyclo(-Val-Sar-Sar-Gly-) (**2**) Precursors

Product Number	Gly	Val	Sar	Sar	Yield [%]
	Boc — OH H —	OBzl			[b])
12	Boc —	OBzl			97
13	Boc —	OH H —	OBzl		98
14	Boc —		OBzl		72
15	Boc —		OH H —	OBzl	99
16	Boc —			OBzl	79
17	Boc —			OH	99
18	Boc —			OPFP	[a])
19	H —			OPFP	[a])

c) cyclo(-D-Ala-Sar-MeLeu-Gly-) (**3**) Precursors

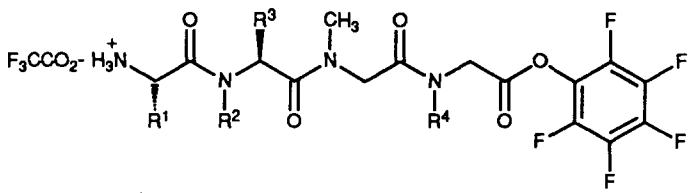
Product Number	D-Ala	Sar	MeLeu	Gly	Yield [%]
	Boc — OH H —	OBzl			
20	Boc —	OBzl			92
21	Boc —	OH H —	OBzl		96
22	Boc —		OBzl		[a])
23	Boc —		OH H —	OBzl	[a])
24	Boc —			OBzl	50[c])
25	Boc —			OH	99
26	Boc —			OPFP	[a])
27	H —			OPFP	[a])

[a]) Carried on without purification.

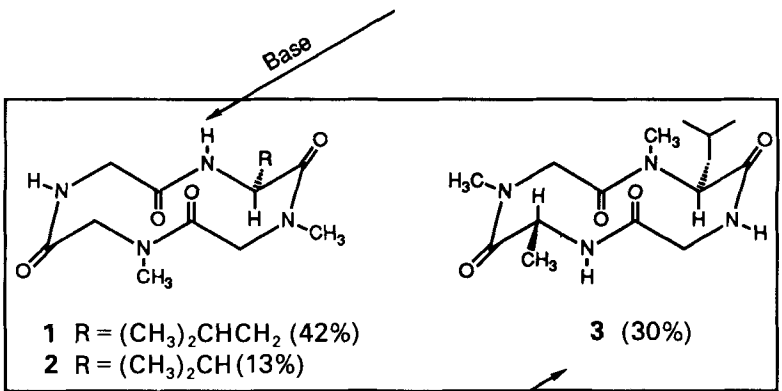
[b]) Coupled *via* the mixed-anhydride method using isobutyl chloroformate and *N*-methylmorpholine in THF/DMF.

[c]) Yield from **21**.

Scheme 3. *Cyclization of the Linear Tetrapeptide Pentafluorophenyl Esters* **11**, **19**, *and* **27** *to the Cyclic Tetrapeptides* **1–3**. High-dilution conditions were employed, with pyridine (20%)/dioxane as solvent, containing 0.8 equiv. of DMAP and 1.5% CF_3CH_2OH.

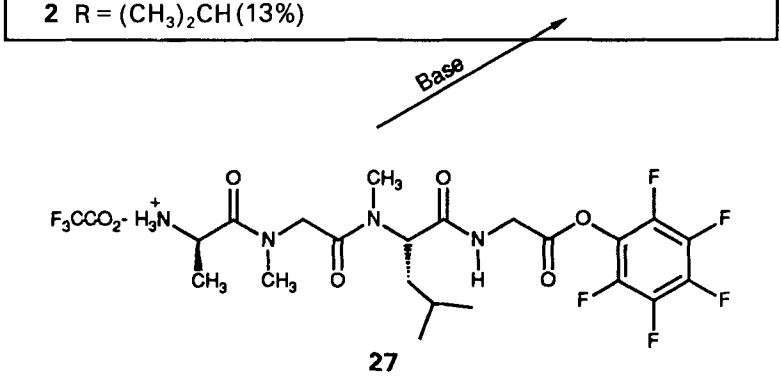


11 $R^1 = (CH_3)_2CHCH_2$, $R^2 = CH_3$, $R^3 = R^4 = H$
19 $R^1 = R^2 = H$, $R^3 = (CH_3)_2CH$, $R^4 = CH_3$



1 $R = (CH_3)_2CHCH_2$ (42%)
2 $R = (CH_3)_2CH$ (13%)

3 (30%)



27

groups up-up-down-down, relative to the average plane of the ring (see **1–3**, *Scheme 3*). See *Sect. 3* for a second conformation of the cyclic tetrapeptides dealt with in this paper.

As noticed previously, the solubility of small peptides in THF, the solvent of choice for the deprotonations, may strongly depend on the presence of salts [15]. We, therefore, determined the solubility of our tetrapeptides, in the absence and presence of LiBr (*Table 2*). Whereas the addition of 4 equiv. of LiBr resulted in the expected [15] increase in solubility of **1** in THF, the opposite was true for tetrapeptides **2** and **3**. To our surprise, we observed an *increased* solubility of **2** and **3**, when samples of the solid peptides and LiBr,

Table 2. *Solubilization of the Cyclic Tetrapeptides* **1–3** *in THF in the Presence of LiBr at Room Temperature* (r.t.) *and* −78°. The ranges for the solubilities were determined by stirring the mixture of the cyclic peptide and LiBr with excess THF overnight (lower number), filtering, evaporating the solution to dryness, and dissolving the residue in a minimum amount of THF (higher number), *cf.* [15].

Equiv. LiCl	Solubility in THF [mg/ml]				
	1	**2**		**3**	
	r.t.	r.t.	78°	r.t.	−78°
0	13	9.8		4.2 to 10	< 2.0
2	10 to 14	3.9	2.2	2.0 to 2.6	8.4
4	93 to 166	1.4	8.0	1.5 to 1.6	8.9
6	84 to 113	1.3	5.2	1.5 to 1.6	8.2

cooled to −78°, were combined with THF[7a]) while stirring. It is remarkable, however, that a heterogeneous mixture of, for instance, **3**, LiBr, and THF does not become homogeneous when cooled from room temperature to −78°. On the other hand, a solution of **2** or **3**, when prepared at −78°, becomes turbid upon warming to room temperature (see the NMR measurements described in the *Exper. Part*). To appreciate the observed effect, it is important to remember *a*) that LiX compounds have different aggregation states at different temperatures (often lower aggregation numbers at lower temperatures! [21–26])[7b]); *b*) that peptides can have different conformations in the solid state, in solutions, and in their complexes with Li salts [13] [25]; and *c*) that the rate of solution may be subject to strong kinetic effects [15] (see the range of concentrations in *Table 2;* for crystal structures of LiX · peptide complexes, see [13] [26]).

3. Alkylation of the Cyclic Tetrapeptides 1–3. – The alkylations were performed in THF, in the presence of at least 2 equiv. of LiBr and 4 equiv. of 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU)[8]). In addition, since crystals of **1–3** contained up to 4% H_2O, the most effective conditions for alkylation required an excess of base. This means that all the results described herein have been obtained with trilithio derivatives of the cyclic peptides in the presence of LiOH (or Li_2O). In contrast to our findings with linear peptides [14], addition of BuLi, prior to the addition of electrophiles, did not results in enhanced yields and selectivities.

The deuteration of **1** in THF afforded a product in 64% yield (*Entry 1, Table 3*), the ^{1}H-NMR spectrum of which indicated a *ca.* 70% D incorporation at the C(5) sarcosine methylene (see formula **28a**, *Fig. 1*)[9]). Only the *outside* proton had been replaced by D, resulting in the (*S*)-configuration. In addition, comparison of the optical rotations of **1** and **28a** (see *Exper. Part*) showed that *no racemization had occurred.*

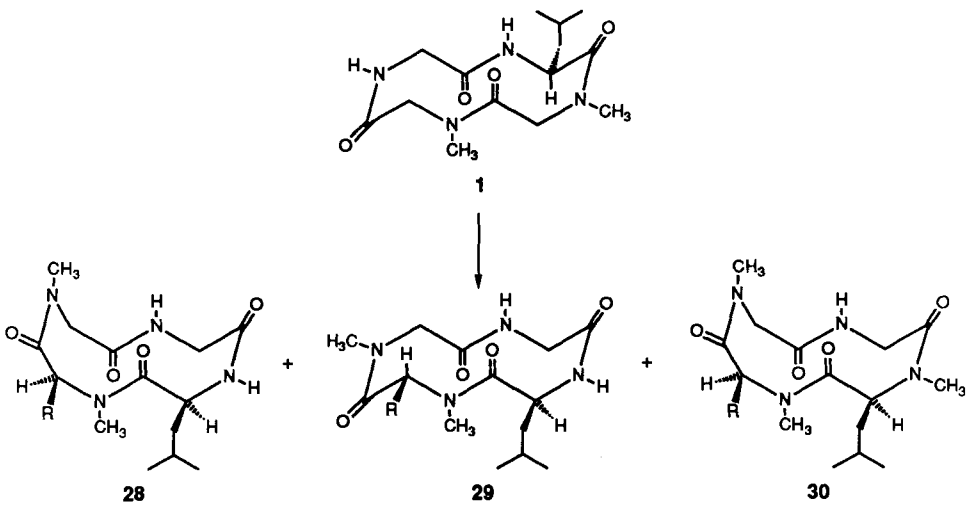
[7a]) As in all cases, the added solvent and added solutions were not precooled, the additions were carried out drop by drop, or with the syringe needle immersed in the reaction mixture; internal *Pt-100* thermometers were used to allow for careful control and maintenance of a given temperature.

[7b]) For examples of mixed aggregates of lithium phenolates and evidence for desolvation of lithium phenolates, see [27].

[8]) DMPU was found to improve the alkylation yields and, on occasion, the solubility of the peptides.

[9]) *Dale* and *Titlestad* first discussed the different proton orientations in cyclic tetrapeptides [6a]. The numbering of the ring atoms is based on this and later work (for a summary, see [7]).

Table 3. *Alkylation of* **1** *with Various Electrophiles in THF at −78° in the Presence of DMPU.* The conformations of the products were determined by DNOE and, in the case of **28b**, by ROESY ^{1}H-NMR spectroscopy.



1

28 + **29** + **30**

a R = D, **b** R = CH_3, **c** R = CH_2OH, **d** R = CH_2=$CHCH_2$.

Entry	Electrophiles	Conditions[a])	Products			
			Type	Yield [%]	**1** [%]	Ratio (**28/29/30**)
1	CF_3CO_2D	*A*	**a**	70	64[b])	only **28a**
2	MeI	*B*	**b**	40	36	only **28b**[c])
3	MeI	*C*	**b**	60	22	7.9:1.0:1.1
4	MeI	*D*	**b**	66	26	6.3:1.0:1.4
5	CH_2O	*E*	**c**	42	10	4.3:1.0[d])
6	CH_2=$CHCH_2Br$	*E*	**d**	25	50	only **28d**
7	$PhCH_2Br$	*E*	–	n.r.	89	–

[a]) *A*) 1. 4 equiv. of LiBr, THF, 4 equiv. of DMPU, −78°, 6.5 equiv. of LDA; 2. 3.4 equiv. of BuLi; 3. 14 equiv. of CF_3CO_2D.
B) 1. 2 equiv. of LiBr, THF, 6 equiv. of DMPU, −78°, 10 equiv. of LiHMDS; 2. 12 equiv. of MeI.
C) 1. 2 equiv. of LiBr, THF, 4 equiv. of DMPU, −78°, 10 equiv. of LDA; 2. 12 equiv. of MeI.
D) 1. 2 equiv. of LiBr, THF, 8 equiv. of DMPU, −78°, 10 equiv. of LDA; 2. 12 equiv. of MeI.
E) 1. 2 equiv. of LiBr, THF, 6 equiv. of DMPU, −78°, 10 equiv. of LDA; 2. electrophile.

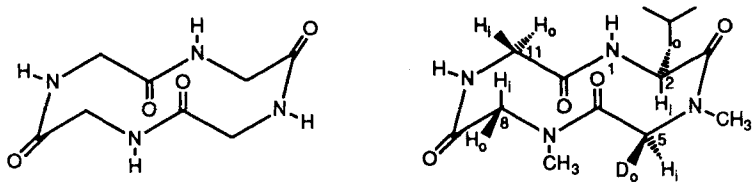
[b]) Sum of deuterated **32a** and non-deuterated **3**; ratio determined by ^{1}H-NMR.

[c]) Trace amounts of **29b** and **30b** were detectable by HPLC.

[d]) Product of type **30** would not be stable in this case!

In contrast to deuteration, alkylation with MeI resulted in a mixture of three products – readily separable by reverse-phase HPLC – consisting of two peptides alkylated at C(5) (**28b** and **29b**; *Table 3*) and one peptide alkylated at both the C(5) and on the leucine N-atom (**30b**)[10]). In contrast to our experience with linear peptides [14], no products resulting from twofold *C*-alkylation were observed with the cyclic peptides. The absolute

[10]) The formation of *N*-alkylated product appears to occur more readily in the presence of a large excess of LDA or other bases such as *sec*-BuLi. This effect has also been observed in some linear peptides [28].



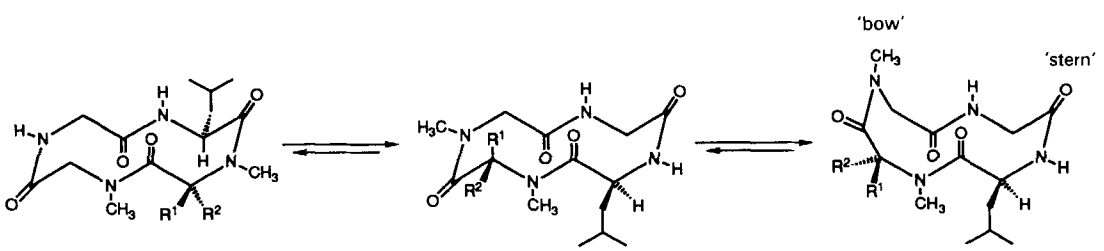
(i and o designate the inner and outer positions, respectively) **28a**

Fig. 1. C_i-*Symmetrical conformation of the unsubstituted backbone of a cyclic tetrapeptide with numbering convention*[9]) *shown for* **28a**

configuration of the newly formed *N*-methylalanine in **28b–30b** was found to be (*S*), (*R*), and (*S*), respectively, by GC comparison with derivatives of authentic (*S*)- and (*R,S*)-*N*-methylalanine [14]. While the more bulky LiHMDS (*Entry 2, Table 3*) tended to provide a larger degree of selectivity, the best yields and product ratios were obtained using LDA as base with 4–8 equiv. of DMPU. Under these conditions, *yields of up to 66%* were achieved (*Entries 3* and *4*, *Table 3*).

The conformations of **28b–30b** and the other products shown in *Table 3* have changed from **1** in that the leucine i-Bu substituent is now at C(5), instead of C(2). While the major product, **28b**, displays several conformations (**A–C**) in D_2O, (D_6)DMSO, and CD_3OD, only conformer **C** is observed in $CDCl_3$ on the NMR time scale. Although the peptide ring is still in a *ctct*-conformation, the C=O groups are now oriented up-up-up-down relative to the plane of the ring. Presumably, this 'boat'-type conformation alleviates unfavorable steric interaction of the newly added substituent with the adjacent coplanar N–Me (conformer **A** of **28b**, *Scheme 4*), while allowing all the substituents to occupy outside positions on the ring[11]).

Scheme 4. *Conformational Interconversion of the Alkylation Products of Cyclic Tetrapeptide* **1**



Conformer **A** ('zigzag') Conformer **B** ('zigzag') Conformer **C** ('boat')

28b $R^1 = CH_3$, $R^2 = H$; **29b** $R^1 = H$, $R^2 = CH_3$

We were able to obtain crystals of **28b** from AcOEt which were suitable for X-ray analysis (see *Fig. 2*). It is intriguing that the solid-state structure, while still being a boat-type conformer, differs from the solution structure in $CHCl_3$ in that the 'bow' of the boat is made up of amino acids 3 and 4 (*Dale* convention[9])) in solution and by amino acids

[11]) For a discussion of the conformational interconversions of cyclic tetrapeptides, see [6c][7][29].

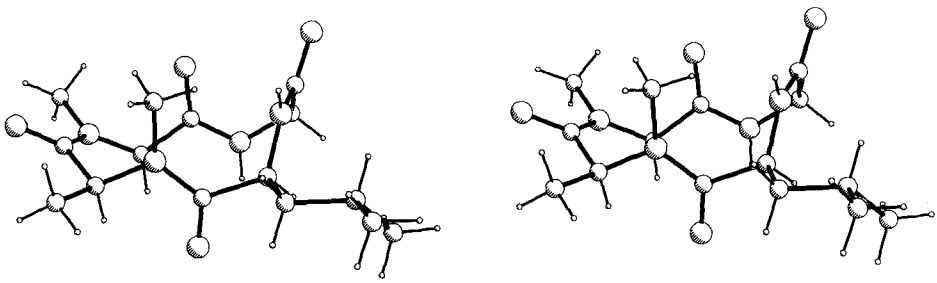


Fig. 2. *PLUTO Stereoplot of [***28b***·EtOAc].* The structure was determined by *V. Gramlich* and *S. Leoni,* at ETH-Zürich.

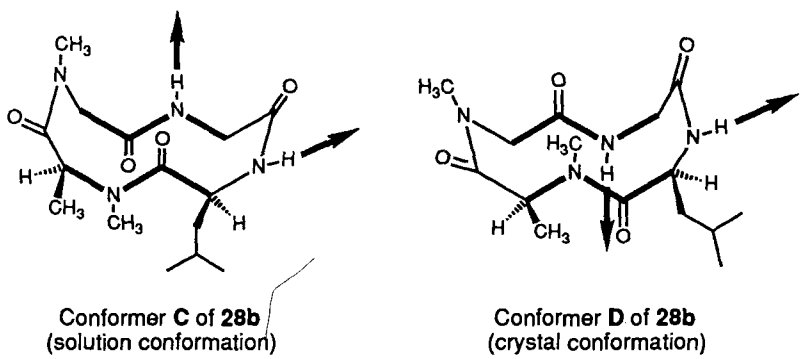


Fig. 3. *The conformations of* **28b** *in $CDCl_3$ solution* (**C**) *and in the Solid State* (**D**, see also *Figs. 2* and *4*). The arrows on NH(1) and NH(4) (*Dale* numbering convention[9]) indicate the approximate directions in which these NH groups can possibly form H-bonds.

1 and 2 in the crystal (*Fig. 3*). The difference in the two conformations is the result of rotation of the entire *trans*-amide groups between Leu and MeAla and between Sar and Gly (see the bold face parts in the formulae of *Fig. 3*). These rotations interchange an N–Me from a bottom to a top position of the boat, and an N–H group from a top to a bottom position. The bow Me and stern Me_2CHCH_2 substituents, now occupy the stern and bow positions, respectively. As can be seen in *Fig. 4*, the conformers **D** form H-bonds between NH(1) and CO(3) as well as between NH(4) and CO(9) (*Dale*-numbering convention[9]). Since we do not see significant differences in *van der Waals* interactions between the two conformers, we assume that the conformational change is caused by packing forces: conformer **D** can make better use of its two NH groups for intermolecular H-bonds (see the arrows in *Fig. 3*).

Of the two minor products (*Table 3*), **30b** exists as two conformers in $CDCl_3$, in a ratio of 3:1, the major conformation appearing to be identical to that of **28b**. In contrast, **29b** exists as only one conformer (in all NMR solvents tested). All substituents are again located on the outside positions of the ring, consistent with literature [7][5]).

Reaction of **1** with CH_2O gave the (*S*)- and (*R*)-*N*-methylserine products **28c** and **29c**, respectively, in a 4.3:1 ratio and 42% yield (*Entry 5, Table 3*). Allylation gave only one product, **28d**, albeit in a significantly lower 25% yield, and reaction of **1** with $PhCH_2Br$ (*Entry 7, Table 3*) resulted in no observable product.

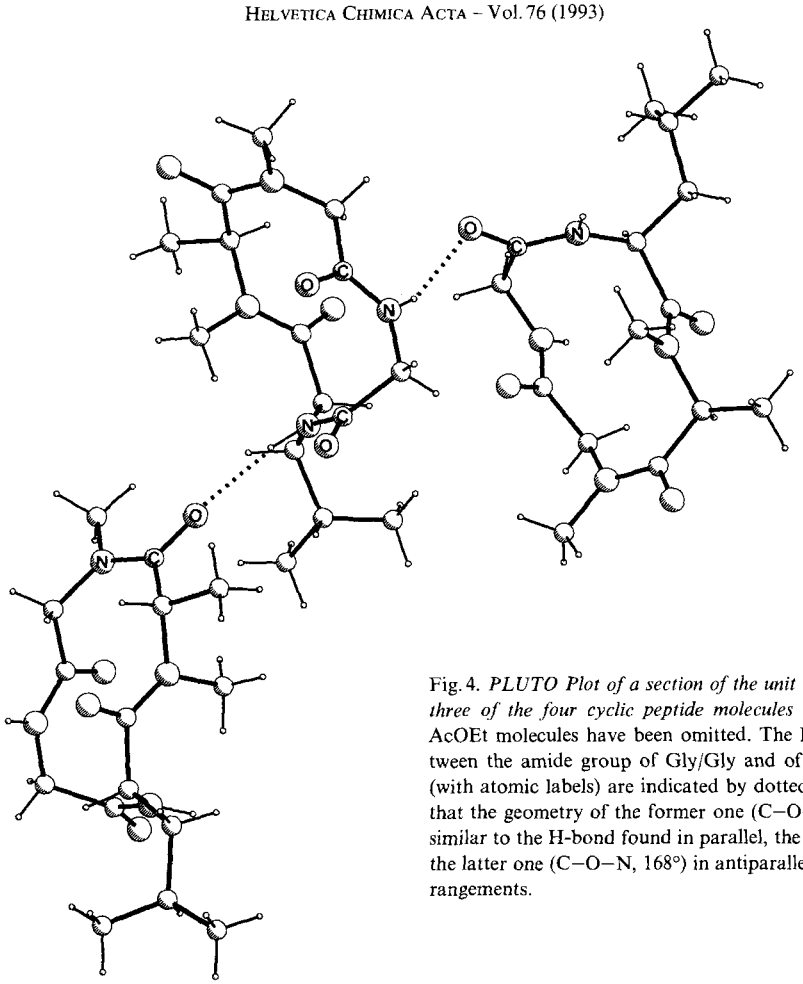
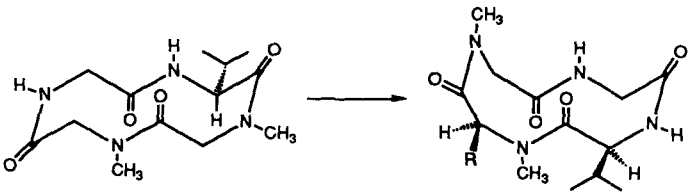


Fig. 4. *PLUTO Plot of a section of the unit cell, showing three of the four cyclic peptide molecules of* **28b**. The AcOEt molecules have been omitted. The H-bonds between the amide group of Gly/Gly and of Leu/MeAla (with atomic labels) are indicated by dotted lines. Note that the geometry of the former one (C–O–N, 127°) is similar to the H-bond found in parallel, the geometry of the latter one (C–O–N, 168°) in antiparallel β-sheet arrangements.

In addition to having different solubility properties than **1**, the valine analogue **2** also exhibited a marked decrease in reactivity. Deuteration with CF_3CO_2D resulted in only a 7.5% D incorporation, even though BuLi was added to deprotonate the $(i\text{-Pr})_2NH$ formed in the peptide lithiation step (*Entry 1, Table 4*). In contrast, alkylation with MeI proceeded to furnish a single product in 20% yield[12]). Reaction of lithiated **2** with CH_2O gave a good yield of the *N*-methylserine product **31c** (*Entry 3, Table 4*), while attempted alkylations with CH_2CHCH_2Br and $PhCH_2Br$ were unsuccessful. As with **28a–d**, the newly formed stereogenic centers in **31a–c** have the (*S*)-configuration, and the conformers of the new cyclic peptides are now, in all cases, a 'boat' shape in $CDCl_3$. Unlike with cyclopeptide **1**, no products other than **31a–c** were isolated, or observed by analytical HPLC of the crude reaction mixtures from **2**.

[12]) Similar observations were made with BocVal-Gly-Leu. Deuteration of this linear peptide in the presence of TMEDA and *sec*-BuLi gave no product, whereas reaction with MeI under identical conditions resulted in a 12% conversion [28]. For a discussion of a similar effect in our work on amino-acid syntheses, see [30].

Table 4. *Alkylation of* **2** *with Various Electrophiles in THF at −78°.* In all cases, a single diastereoisomer was formed.



2 **31**

a R = D, **b** R = CH_3, **c** R = CH_2O

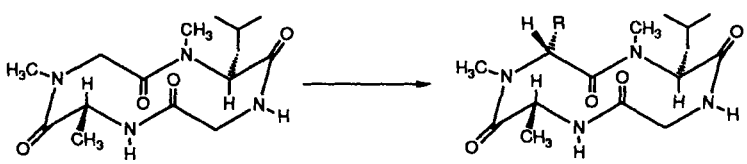
Entry	Electrophiles	Conditions[a])	Products		
			Type	Yield [%]	Recovered **2** [%]
1	CF_3CO_2D	*A*	**a**	7.5	72[b])
2	MeI	*B*	**b**	20	48
3	CH_2O	*C*	**c**	36	30
4	CH_2=$CHCH_2Br$	*C*	–	n.r.	82
5	$PhCH_2Br$	*B*[c])	–	n.r.	80

[a]) *A*) 1. −78°, 12.5 equiv. of LiBr, THF, 5 equiv. of LDA; 2. 3.0 equiv. of BuLi; 3. 14 equiv. of CF_3CO_2D.
B) 1. −78°, 14 equiv. of LiBr, THF, 4 equiv. of LDA; 2. 12 equiv. of MeI.
C) 1. −78°, 12.5 equiv. of LiBr, THF, 5 equiv. of LDA; 2. 12 equiv. of electrophile.

[b]) Sum of deuterated **31a** and non-deuterated **2**; ratio determined by ^{1}H-NMR.

[c]) Benzylation was attempted in the presence and absence of DMPU.

Table 5. *Alkylation of* **3** *with Various Electrophiles in THF at −78°.* In all cases, a single diastereoisomer was formed.



3 **32**

a R = D, **b** R = CH_3, **c** R = CH_2OH, **d** R = CH_2=$CHCH_2$, **e** R = $PhCH_2$

Entry	Electrophiles	Conditions[a])	Products		
			Type	Yield [%]	Recovered **3** [%]
1	CF_3CO_2D	*A*	**a**	65	90[b])
2	MeI	*B*	**b**	46	18
3	CH_2O	*B*	**c**	34	None
4	CH_2=$CHCH_2Br$	*B*	**d**	70	17
5	$PhCH_2Br$	*B*	**e**	34	19

[a]) *A*) 1. −78°, 13.5 of equiv. LiBr, THF, 4 equiv. of DMPU, 3.4 equiv. of LDA; 2. 3.0 equiv. of BuLi; 3. 14 equiv. of CF_3CO_2D.
B) 1. −78°, 12.5 equiv. of LiBr, THF, 6 equiv. of DMPU, 5 equiv. of LDA; 2. 12 equiv. of electrophile.

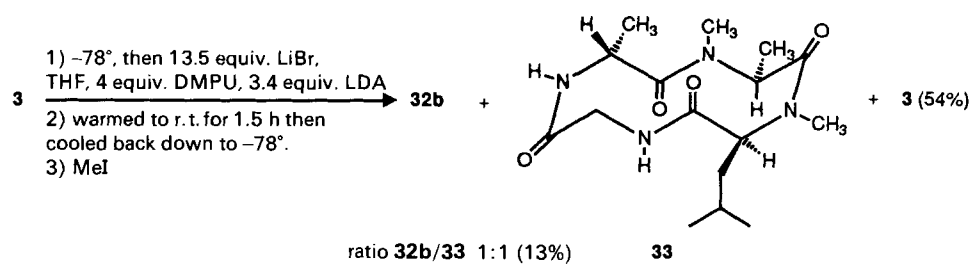
[b]) Sum of deuterated **32a** and non-deuterated **3**; ratio determined by ^{1}H-NMR.

Results of the alkylation of **3** are presented in *Table 5*. *Again, in all cases only one product was observed!* Deuteration gave a product in 90% yield with 65% D incorporation (*Entry 1, Table 5*). The ^{1}H-NMR spectrum indicates that the outer proton at C(11) has been exclusively replaced by D as shown for **32a**, generating an (*R*)-configuration at this center. Other electrophiles gave equally high selectivities in good-to-excellent yields (all unoptimized) for this transformation. Methylation (*Entry 2*) produced **32b** containing (*R*)-*N*-methylalanine in 46% yield. Particularly noteworthy is the 70% yield of **32d** obtained with CH_2=$CHCH_2Br$ (*Entry 4, Table 5*), suggesting that the lithiated cyclopeptide **3** is significantly more reactive than Li derivatives of either **1** or **2**. As a result, it is not surprising that **3** could also be readily converted to the (*R*)-*N*-methylphenylalanine product **32e** in 34% yield (*Entry 5*). Unlike the products derived from **1** and **2**, **32a–e** all have conformations identical with those of the starting peptide **3** in all solvents tested (*e.g.*, D_2O, $CDCl_3$, and CD_3OD), with no minor conformers visible by NMR spectroscopy.

4. Surprising Reversal of Selectivity by Warming and Cooling the Enolates of 1 and 3. – During an early alkylation experiment with cyclopeptide **1**, a heterogeneous solution resulted upon addition of 3.7 equiv. of LDA at –78°. In an attempt to obtain a homogeneous reaction mixture, the peptide/LDA solution was warmed to room temperature for a short period of time, followed by reaction with MeI at –78°. *Based on HPLC analysis of the resulting reaction mixture and on product isolation,* **29b** *was now the major product!* Although the yield was significantly lower (**28b** and **29b**: 8%, recovered **1**: 39%), the ratio of **28b**/**29b** was now 1:4.3 rather than 7.9:1, obtained when the mixture had not been warmed prior to electrophile addition (*cf. Table 3*). To confirm that the selectivity reversal was not due to loss of **28b** during workup this experiment was repeated. A solution of **1**, LiBr, DMPU, THF, and LDA was warmed to room temperature for 1.5 h, followed by cooling back to –78° and addition of the electrophile. Workup of this reaction mixture under identical conditions to those giving high yields, as specified in *Table 3*, gave recovered **1** (48%) and **29b** (12%). Analytical HPLC indicated an approximate ratio of 1:3 for **28b**/**29b**; however, none of the former product was isolated due to poor column resolution.

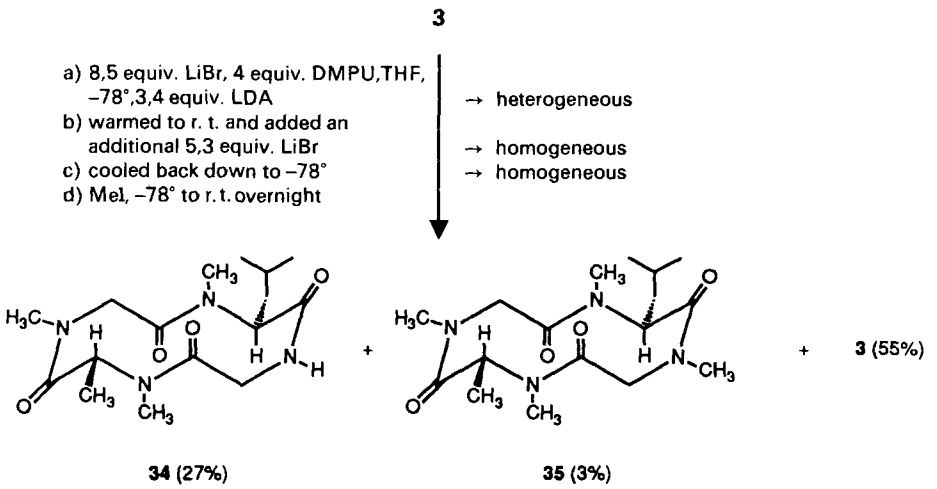
It was of interest to determine, whether this effect could be repeated with another cyclic peptide. Indeed, when a similar experiment was performed with the cyclopeptide **3**, a new product was formed in addition to **32b** in a 1:1 ratio containing (*S*)-*N*-methylalanine (**33**, *Scheme 5*). Although the yield was again much lower than when running the reaction solely at –78°, *this new product had never been observed under the latter conditions.* Conformational analysis by DNOE-NMR spectroscopy suggests that **33** exists in the *ctct*-conformation, as shown in *Scheme 5*, in which the *N*-methylleucine substituent is now at C(5), thus allowing the new (*S*)-*N*-methylalanine substituent to occupy the outside position on C(2).

Scheme 5. *Alkylation of* **3** *after Warming the Enolate to Room Temperature.* The electrophile was added to the reaction solution at –78°.



Another surprising change in regioselectivity was observed when **3** was 'solubilized' at room temperature, followed by repeating the above alkylation procedure (*Scheme 6*). A heterogeneous mixture containing **3** – obtained by adding THF, LiBr, and DMPU at room temperature – was cooled to –78°, treated with LDA and allowed to warm to room temperature, until the solution had cleared. After cooling back down to –78°, MeI was

Scheme 6. *Alkylation of an Initially Heterogeneous Solution of* **3**. When the reaction solution was quenched at −78°, no product was obtained and **3** was recovered in 87% yield.



added and the reaction mixture stirred overnight. Quenching this solution at −78°, gave only recovered starting material. However, when such a reaction mixture was warmed to room temperature overnight, two new products were isolated resulting from alkylation of the alanine N-atom (product **34**), and of both the alanine and the glycine N-atoms (product **35**). No product resulting from *C*-alkylation was observed under these conditions.

According to ^{1}H-NMR analysis, each of the two new compounds exists in only one conformation, identical to that of the starting material **3**.

5. Comparison of Alkylation and Linear Synthesis Methods: Synthesis of Cyclic Tetrapeptides 28b and 29b from Open-Chain Precursors. – To compare yields of the two methods of cyclic-tetrapeptide synthesis presented in *Scheme 2*, we prepared **28b** and **29b** *via* stepwise synthesis and cyclization. Assembly of the amino-acid components is shown in *Table 6* (intermediates **36**, **37**, **39**–**43**, and **38**, **45**–**48**, respectively). Due to the fortuitous epimerization upon coupling the intermediate dipeptide **37** with the benzyl ester of

Table 6. *Synthesis of the Linear Precursors of the Cyclic Tetrapeptides* **28b** *and* **29b**. The coupling steps were accomplished as described in *Table 1*.

a) 'Authentic' cyclo(-Leu-MeAla-Sar-Gly-) (**28b**) Precursors

Product Number	Leu	MeAla	Sar	Gly	Yield [%]
	Boc—OH	H—OBzl			
36	Boc—	—OBzl			86
37	Boc—	—OH	H—OBzl		99
39	Boc—		—OBzl		74[a])
40	Boc—		—OH	H—OBzl	99[b])
41	Boc—			—OBzl	90[c])
42	Boc—			—OH	99
43	Boc—			—OPFP	35
44	H—			—OPFP	[d])

Table 6 (cont.)

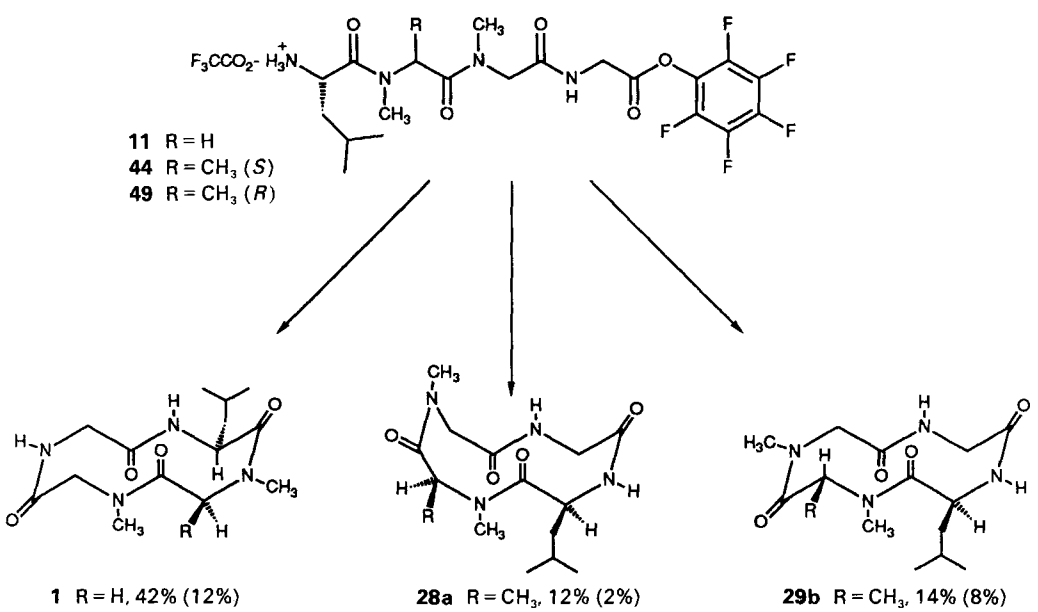
b) 'Authentic' cyclo(-Leu-D-MeAla-Sar-Gly-) (**29b**) Precursors

Product Number	Leu	(D)-MeAla	Sar	Gly	Yield [%]
38	Boc		OBzl		[c])
45	Boc		OH	H—OBzl	99[b])
46	Boc			OBzl	94
47	Boc			OH	99
48	Boc			OPFP	[d])
49	H			OPFP	[d])

[a]) Mixture of (LL)- and (DL)-diastereoisomers were carried on without separation.
[b]) Coupled *via* the mixed-anhydride method using isobutyl chloroformate and *N*-methylmorpholine in THF/DMF.
[c]) Reaction carried out with purified (LL)-diastereoisomer.
[d]) Carried on without purification.
[e]) Obtained by chromatographic separation from a mixture of **38** and **39**.

sarcosine (*Table 6, a*), both diastereoisomers (*S,S*)-**44** (→**28b**) and (*R,S*)-**49** (→**29b**) were obtained. Recall that the cyclization of the linear peptide **11**, with only one side chain, produced the cyclic tetrapeptide **1** in 42% yield (*Scheme 3*, with an overall yield of 12% from Boc-Leu). In contrast, the tetrapeptides **44** and **49**, having an additional substituent, cyclize to give **28b** and **29b**, respectively, in significantly lower yield (*Scheme 7*).

Scheme 7. *Synthesis of 'Authentic'* **28b** *and* **29b** *by Cyclization.* Cyclizations were performed as described in *Scheme 3*. The yields given in brackets are the overall yields of the cyclic peptides from Boc-leucine.



Although these yields have not been optimized, the results are consistent with those reported in the literature [11a–c]. In addition to the lower yields of cyclization caused by increasing the degree of substitution of the cyclization precursor, another disadvantage of traditional peptide modification is the time and cost of a linear synthesis, not to mention of the cyclization! Thus, bypassing the synthesis and cyclization, by modifying the cyclic peptide directly, is considerably more efficient.

6. Speculations on the Possible Mechanisms. – The results described in the previous sections demonstrate that we have generated lithiated amides and sarcosine enolates within the cyclic peptides. When we began this investigation, we were concerned that such nucleophilic moieties on one side of the peptide ring might attack a transannular amide C=O group with formation of an N–C or C–C bond[13]). However, we have no indication for such, possibly self-destructing, side reactions under the currently applied low-temperature conditions[14])[15]).

The stereochemical outcome of the alkylation of sarcosine residues with electrophiles, is formally a replacement of an outer H-atom in the α-position of the C=O group with retention of configuration. Although the structure of the species involved may be extremely complicated – amide enolates [33] [34] as well as lithiated amides [35] [36] are aggregated, LiBr can form mixed aggregates with the lithiated peptide [13] [27], DMPU forms complexes with lithium enolates [37], and the *sec*-amine generated in the deprotonation step may form H-bonded complexes with lithium enolates [34] – we are tempted to make the following simple assumptions compatible with the experimental results: *a*) The conformation of the cyclic peptide backbone, as determined by NMR spectroscopy, is preserved, when we first remove the two NH protons and then an outer sarcosine CH proton. *b*) The trilithio derivative thus formed from the cyclic peptide (*cf. Fig. 5*) retains

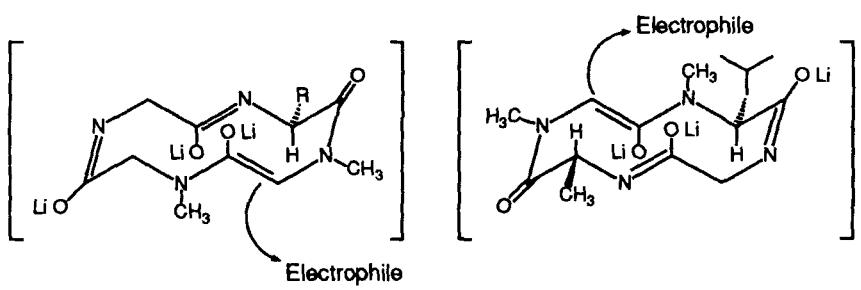


Fig. 5. *Proposed structures of the trilithio derivatives of* **1**, **2**, *and* **3**. There are two aza-enolate moieties, one with a (*Z*)- and one with an (*E*)-configuration, and a (*Z*)-enolate in each. The conformations are derived from the major solution conformation of **1** and **2**, and from the only observed solution conformation of **3**.

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[13]) *Cf.* cyclol formation in cyclic tripeptides [31][32]. The distance between the opposite amide planes across the ring in **28b** is smaller than 3 Å.

[14]) The product yields were somewhat lower in the experiments in which the solutions of the lithiated cyclopeptides were warmed to room temperature!

[15]) In the structures of the peptides themselves (NMR and X-ray measurements) the N-atoms and C=O groups are transannular neighbors, but not potential enolate β-C-atoms and C=O groups.

its conformation, as long as the solution is not warmed. *c*) The electrophile approaches from the ouside of the ring, the same face from which the proton had been abstracted.

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Experimental Part

1. *General.* All reactions were carried out under positive Ar pressure in oven- or flame-dried glassware. CH_2Cl_2, AcOEt, and hexane were distilled over P_2O_5; Et_2O was distilled over KOH/$FeSO_4$. MeOH, EtOH, and $CHCl_3$ were purchased from *Fluka* (*puriss.*). (i-Pr)$_2$NH was distilled from CaH_2 prior to use. DMPU (*BASF*) was distilled from CaH_2 (110°/5 torr) and stored over activated molecular sieves (4 Å). LiBr (*Fluka, purum.*) was dried at 150–160° under high vacuum for 3 h prior to use. For alkylations, a stock soln. of LiBr in THF (0.69M) was prepared and stored in the dark under Ar pressure. Unless otherwise noted, org. extracts were dried over $MgSO_4$, filtered, and evaporated using a rotary evaporator. Basic *Dowex* refers to *Fluka Dowex Ion Exchange Resin 1 × 8* (20–50 mesh), washed with 6M NaOH, H_2O, and MeOH. Acidic *Dowex* refers to *Fluka Dowex Ion Exchange Resin 50 × 8* (20–50 mesh), washed with 6M HCl, H_2O, and MeOH. Dry THF for alkylations was freshly distilled from K under Ar. BuLi (*Chemetall Gesellschaft*, 15% in hexane) was titrated according to the procedure of *Ronald* and coworkers [38] using 2,5-dimethoxybenzyl alcohol as indicator. Electrophiles (MeI, CH_2=$CHCH_2Br$, and $PhCH_2Br$) were filtered through activated basic aluminum oxide (*Woelm*) prior to use.

Flash chromatography (FC) was performed on *Fluka* silica gel *60*. Radial chromatography separations were performed by using a *Harrison Research Chromatotron* on plates of 1-, 2-, or 4-mm thickness made with *Merck* silica gel *60-PF$_{254}$*-containing gypsum. TLC: *Merck* silica gel *60 F$_{254}$* anal. plates; detection by UV and/or by placing in a Cl_2 tank for 5 min, then staining with a soln. of bis[4-(dimethylamino)phenyl]methane (TDM) stain [39]. HPLC: Anal.: *Kontron* equipment using a *Macherey-Nagel* reverse phase *Nucleosil® 100-5 C$_8$*, or *100-7 C$_4$* column, 250 × 4 mm ID. Prep.: *Knauer* equipment using a *Knauer* reverse phase *C$_8$ Lichrosorb* 7-μm column, *Macherey-Nagel* reverse phase *Nucleosil® 100-7 C$_8$*, and *500-7 C$_4$* columns. Hydrolyses and derivatizations of the peptides were performed as described in [14]. GC: *Chirasil-Val®* column (*Macherey-Nagel*, 25 m, 0.4 mm), *Carlo-Erba-Fractovap 4160-HR GC*; temp. program: 5 min 160°, 2°/min, 45 min 200°, or isothermal at 155°. M.p.: *Büchi-510* apparatus or *Culatti* apparatus; uncorrected. Optical rotations: 10 cm, 1-ml cell, *Perkin-Elmer 241* polarimeter at r.t. (ca. 22°). IR: *Perkin-Elmer 983* or *PE FT-IR 1600* spectrometers. ^{1}H- and ^{13}C-NMR: *Bruker WM-400*, *Bruker WM-300*, or *Varian XL-300* and *Gemini 200* spectrometers. Where the existence of rotamers complicate the ^{1}H- and ^{13}C-NMR spectra, unless otherwise noted, only the peaks of the major component are listed. High-temp. (180°) NMR was performed on the *Bruker WM-300* spectrometer equipped with a water-cooled high-temp. ^{1}H,^{13}C- dual probehead. FAB-MS: *VG-ZAB2-SEQ* in a 3-nitrobenzyl-alcohol matrix in *m/z* (% of base peak).

2. *Cyclization Precursors Boc-Leu-Sar-OCH$_2$Ph*(**4**). To a soln. of 37.0 g (148 mmol) of Boc-Leu (*Bachem*) in 740 ml of CH_2Cl_2, cooled to −18°, was added Et(i-Pr)$_2$N (50.8 ml, 297 mmol), followed by BOP-Cl (41.56 g, 163 mmol). After stirring the heterogeneous mixture for 30 min, a soln. of sarcosine benzyl ester toluene-4-sulfonate (57.37 g, 163 mmol) and Et(i-Pr)$_2$N (25.9 ml, 151 mmol) in 580 ml CH_2Cl_2, was added dropwise over 2 h. The mixture was then allowed to warm to r.t. overnight (12 h) while stirring. The resulting clear, pale-yellow soln. was partially concentrated and washed twice with both 0.1N H_2SO_4 and $NaHCO_3$. The combined aq. phases were washed with CH_2Cl_2 and the combined org. phases dried, filtered, and concentrated. Purification by FC (3:1→2:1 hexane/AcOEt) gave **4** as a colorless oil, 41.12 g (71%). $[\alpha]_D = -32.1$ (*c* = 0.28, EtOH). IR (thin film): 3306*w* (br.), 2957*m*, 1748*s*, 1707*s*, 1651*s*, 1498*m*, 1174*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.92 (*d*, *J* = 6.6, 3 H); 0.99 (*d*, *J* = 6.5, 3 H); 1.40–1.47 (*m*, 2 H); 1.43 (*s*, 9 H); 1.75 (*m*, 1 H); 3.14 (*s*, 3 H); 3.80 (*d*, *J* = 17, 1 H); 4.70 (*m*, 1 H); 5.16 (*s*, 2 H); 5.20 (*m*, 1 H); 7.36 (*s*, 5 H). FAB-MS: 415.3 (40, $[M + 23]^+$, $C_{21}H_{32}N_2O_5Na^+$), 393.3 (40, $[M + 1]^+$, $C_{22}H_{32}N_2O_5^+$), 337.2 (30), 293.2 (42), 180.1 (37), 130.1 (26), 91.0 (100).

Boc-Leu-Sar-OH (**5**). To a soln. of **4** (41.12 g, 105 mmol) in MeOH (200 ml) were added 2.06 g of 10% Pd/C (*Fluka*). The reaction flask was evacuated and purged twice with H_2, and the soln. stirred under an atmosphere of H_2 overnight. Filtration through *Celite*, followed by concentrating, afforded 30.68 g (97%) of **5** as a colorless foam, which was carried on without further purification. $[\alpha]_D = -29.7$ ($c = 0.30$, EtOH). IR (thin film): 3550–2500*m* (br.), 3315*m*, 2959*s*, 1713*s*, 1640*s*, 1504*m*, 1408*m*, 1168*s*, 773*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.88 (*d*, $J = 6.6$, 3 H); 0.89 (*d*, $J = 6.5$, 3 H); 1.38 (*s*, 9 H); 1.39–1.47 (*m*, 2 H); 1.68 (*m*, 1 H); 2.99 (br. *s*, 3 H); 4.03 (*m*, 2 H); 4.45 (*m*, 1 H); 6.12 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 180°): 21.6; 22.8; 24.2; 28.2; 49.0; 49.9; 78.3; 154.9; 169.9; 172.5. FAB-MS: 627.4 (8, $[2M + 23]^+$, $C_{28}H_{52}N_4O_{10}Na^+$), 325.2 (68, $[M + 23]^+$, $C_{14}H_{26}N_2O_5Na^+$), 303.2 ($[M + 1]^+$, $C_{14}H_{27}N_2O_5^+$), 247.1 (79), 203.1 (79), 86.0 (100).

Boc-Leu-Sar-Sar-OCH$_2$Ph (**6**). As described for **4**, with **5** (30.68 g, 103 mmol), Et(i-Pr)$_2$N (34.7 ml, 203 mmol), BOP-Cl (28.41 g, 112 mmol), 507 ml CH_2Cl_2, sarcosine benzyl ester toluene-4-sulfonate (39.22 g, 112 mmol), Et(i-Pr)$_2$N (19.4 ml, 114 mmol), and 580 ml of CH_2Cl_2. After extractive workup, as for **4**, FC (50%→75% AcOEt/hexane, sample applied to column with $CHCl_3$) gave the product in two fractions. ^{1}H-NMR of both fractions were identical. The product was a colorless foam (44.1 g, 94%). $[\alpha]_D = -20.9$ ($c = 0.98$, EtOH). IR (thin film): 3306*w* (br.), 2958*m*, 1748*s*, 1707*s*, 1650*s*, 1490*s*, 1175*s*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.87 (*d*, $J = 6.6$, 6 H); 1.37 (*s*, 9 H); 1.45–1.40 (*m*, 2 H); 1.66 (*m*, 1 H); 2.93 (br. *s*, 3 H); 2.98 (br. *s*, 3 H); 4.00–4.50 (*m*, 5 H); 5.15 (*s*, 2 H); 6.08 (br. *d*, $J = 7.9$, 1 H); 7.34 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 180°): 21.6; 22.8; 24.2; 28.2; 35.0; 35.2; 49.0; 50.4; 66.1; 78.3; 127.7; 127.9; 128.3; 135.8; 155.0; 168.8; 168.3; 172.5. FAB-MS: 486.3 (36, $[M + 23]^+$, $C_{24}H_{37}N_3O_6Na^+$), 464.3 (26, $[M + 1]^+$, $C_{24}H_{38}N_3O_6^+$), 364.3 (46), 251.1 (60), 229.1 (67), 91.0 (100).

Boc-Leu-Sar-Sar-OH (**7**). As described for **5**, with **6** (44.0 g, 94.9 mmol), MeOH (200 ml), and 10% Pd/C (2.20 g): 34.98 g (99%) of **7**. $[\alpha]_D = -23.4$ ($c = 1.0$, EtOH). IR (thin film): 3700–2700*m* (br.), 3324*w* (br.), 2958*m*, 1710*s*, 1650*s*, 1494*m*, 1407*m*, 1168*m*, 732*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.879 (*d*, $J = 6.6$, 3 H); 0.885 (*d*, $J = 6.2$, 3 H); 1.38 (*s*, 9 H); 1.40–1.50 (*m*, 2 H); 1.66 (*m*, 1 H); 2.94 (br. *s*, 6 H); 4.00–4.50 (*m*, 5 H); 6.06 (br. *d*, $J = 8$, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 180°): 21.6; 22.9; 24.2; 28.2; 34.8; 35.2; 49.0; 49.7; 78.2; 154.9; 168.1; 169.9; 172.5. FAB-MS: 396.1 (84, $[M + 23]^+$, $C_{17}H_{31}N_3O_6Na^+$), 374.1 (30, $[M + 1]^+$, $C_{17}H_{32}N_3O_6^+$), 274.0 (57), 229.0 (71), 161.0 (90), 86.0 (60).

Boc-Leu-Sar-Sar-Gly-OCH$_2$Ph (**8**). As described for **4**, with **7** (27.17 g, 72.8 mmol), Et(i-Pr)$_2$N (24.9 ml, 146 mmol), BOP-Cl (20.37 g, 80.0 mmol), CH_2Cl_2 (362 ml), glycine benzyl ester toluene-4-sulfonate (27.0 g, 80.0 mmol), Et(i-Pr)$_2$N (13.9 ml, 81.5 mmol), and CH_2Cl_2 (285 ml). Purification by FC (2%→3%→5% MeOH/CH_2Cl_2) gave 17.68 g (47%) of **8** as a colorless foam. $[\alpha]_D = -20.5$ ($c = 1.0$, EtOH). IR (thin film): 3306 *m* (br.), 2957*m*, 1749*s*, 1650*s* (br.), 1523*s*, 1497*s*, 1175*s*, 736*w*, 698*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.88 (*d*, $J = 6.5$, 6 H); 1.38 (*s*, 9 H); 1.40–1.50 (*m*, 2 H); 1.66 (*m*, 1 H); 2.86 (*s*, 3 H); 2.90 (*s*, 3 H); 3.93 (*d*, $J = 5.8$, 2 H); 3.99 (*s*, 2 H); 4.20–4.45 (*m*, 3 H); 5.13 (*s*, 2 H); 6.08 (br. *s*, 1 H); 7.33 (*m*, 5 H); 7.98 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 180°): 21.7; 22,9; 24.2; 28.2; 34.8; 35.1; 49.0; 51.0; 65.9; 78.3; 127.6; 127.8; 128.2; 136.0; 155.0; 168.2; 168.4; 172.5. FAB-MS: 543.3 (35, $[M + 23]^+$, $C_{26}H_{40}N_4O_7Na^+$), 521.3 (9, $[M + 1]^+$, $C_{26}H_{41}N_4O_7^+$), 443.2 (8), 421.2 (36), 308.1 (33), 237.1 (35), 229.1 (49), 91.0 (64).

Boc-Leu-Sar-Sar-Gly-OH (**9**). As described for **5**, with **8** (17.52 g, 33.7 mmol), MeOH (100 ml), and 10% Pd/C (0.876 g): 14.36 g (99%) of **8**. $[\alpha]_D = -24.8$ ($c = 1.0$, EtOH). IR (thin film): 3308*m* (br.), 2959*m*, 1648*s* (br.), 1528*m*, 1496*m*, 1168*m*, 732*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.88 (*d*, $J = 6.5$, 6 H); 1.38 (*s*, 9 H); 1.40–1.50 (*m*, 2 H); 1.66 (*m*, 1 H); 2.92 (br. *s*, 3 H); 3.79 (*d*, $J = 5.7$, 2 H); 3.98 (*s*, 2 H); 4.20–4.45 (*m*, 3 H); 6.06 (br. *d*, $J = 7$, 1 H); 7.79 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 180°): 21.7; 22.9; 24.2; 28.2; 34.8; 35.4; 49.0; 51.0; 78.3; 155.0; 168.2; 170.4; 172.5. FAB-MS: 453.3 (40, $[M + 23]^+$, $C_{19}H_{34}N_4O_7Na^+$), 431.2 (7, $[M + 1]^+$, $C_{19}H_{35}N_4O_7^+$), 331.1 (25), 229.1 (39), 218 (34).

Boc-Leu-Sar-Sar-Gly-OPFP (**10**). To a soln. of **8** (6.88 g, 16 mmol) and pyridine (50 ml) at 0° was added pentafluorophenol trifluoroacetate (5.38 g, 19.2 mmol, prepared according to the procedure of *Sakakibara* and *Inukai* [40]), while stirring. The soln. was allowed to warm to r.t. and stirred overnight. After removing the pyridine on a rotary evaporator, the resulting yellow oil was dissolved in Et_2O and washed in rapid succession with H_2O, twice with 5% citric acid, sat. aq. NaCl, twice with sat. aq. $NaHCO_3$, and then saturated aq. NaCl. The org. phase was then dried and concentrated to give **10** as a yellow foam (8.38 g, 88%) which was used without further purification.

Leu-Sar-Sar-Gly-OPFP Trifluoroacetate (**11**). To a soln. of the crude **10** in CH_2Cl_2 (50 ml) at 0° were added 50 ml of CF_3COOH. After 1 h, the soln. was warmed to r.t., stirred and additional 30 min, concentrated, and dried *in vacuo*. The resulting orange-brown oil was stored at −20° until cyclization.

Boc-Gly-Val-OCH$_2$Ph (**12**). To a soln. of Boc-glycine (24.0 g, 137 mmol) in 650 ml of THF at −15° was added *N*-methylmorpholine (NMM; 15.1 ml, 137 mmol), and isobutyl chloroformate (17.9 ml, 137 mmol). A soln. of valine benzyl ester toluene-4-sulfonate (52.6 g. 138 mmol) and NMM (15.2 ml, 138 mmol) in DMF (260 ml) was

then added dropwise. Following the addition, the soln. was stirred for 30 min at −15° and 30 min at r.t., then concentrated under vacuum. The concentrate was dissolved in AcOEt, washed twice with 5% citric acid, sat. aq. $NaHCO_3$, and once with sat. aq. NaCl. The combined aq. layers were washed twice with AcOEt. The combined org. layers were then dried and concentrated to give a colorless, viscous oil which was used without further purification: 48.5 g (97%). $[\alpha]_D = -13.9$ ($c = 0.87$, EtOH). IR (thin film): 3313*m* (br.), 2974*m*, 1718*s*, 1677*s*, 1523*s*, 1174*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86 (*d*, $J = 6.9$, 3 H); 0.92 (*d*, $J = 6.9$, 3 H); 1.45 (*s*, 9 H); 2.19 (*m*, 1 H); 3.82 (*m*, 2 H); 4.60 (*dd*, $J = 8.9$, 4.8, 1 H); 5.16 (*ABq*, $\nu_A = 5.19$, $\nu_B = 5.14$, $J = 12.2$, 2 H); 5.24 (br. *s*, 1 H); 6.71 (br. *d*, $J = 8.3$, 1 H); 7.35 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.5 (*q*); 18.9 (*q*); 28.3 (*q*); 31.6 (*d*); 44.5 (*t*); 57.0 (*d*); 67.1 (*t*); 80.3 (*s*); 128.3 (*d*); 128.4 (*d*); 128.6 (*d*); 135.3 (*s*); 156.0 (*s*); 169.5 (*s*); 171.6 (*s*). FAB-MS: 387.2 (15, $[M + 23]^+$), 365.2 (21, $[MH]^+$), 309.1 (78), 265.1 (41), 91 (100).

Boc-Gly-Val-OH (**13**). As described for **5**, with **12** (48.2 g, 132 mmol), MeOH (350 ml), and 10% Pd/C (2.47 g): 35.6 g (98%) of **13** as a colorless foam. $[\alpha]_D = +14.3$ ($c = 1.0$, EtOH). IR (thin film): 3600*m* (br.), 3333*m*, 2974*m*, 1723*s*, 1662*s*, 1533*m*, 1164*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93 (*d*, $J = 6.8$, 3 H); 0.97 (*d*, $J = 6.9$, 3 H); 1.46 (*s*, 9 H); 2.25 (*m*, 1 H); 3.79 (*m*, 1 H); 3.95 (*m*, 1 H); 4.55 (*m*, 1 H); 5.54 (br. *s*, 1 H); 6.99 (br. *s*, 1 H); 7.27–7.80 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.6 (*q*); 19.0 (*q*); 28.3 (*q*); 31.0 (*d*); 44.3 (*t*); 57.1 (*d*); 80.6 (*s*); 156.5 (*s*); 170.3 (*s*); 174.5 (*s*). FAB-MS: 297.1 (84, $[M + 23]^+$), 275.1 (26, $[MH]^+$), 219.1 (100), 197.1 (28), 175.1 (39), 118.1 (26), 72.0 (68).

Boc-Gly-Val-Sar-OCH$_2$Ph (**14**). To a soln. of sarcosine benzyl ester toluene-4-sulfonate (49.9 g, 142 mmol) in CH_2Cl_2 (500 ml) at 0° was added **13** (35.4, 129 mmol) in CH_2Cl_2 (500 ml). After cooling the soln. to −15°, $Et(iPr)_2N$ (66.5 ml, 387 mmol) and BOP-Cl (36.5 g, 142 mmol) were added in succession. The soln. was then allowed to warm to r.t. and stirred for 4 h. The resulting clear soln. was washed twice with 5% citric acid, sat. aq. $NaHCO_3$, and once with sat. aq. NaCl. The combined aq. layers were washed twice with CH_2Cl_2. The combined org. layers were then dried and concentrated. Purification by FC (3%→5% MeOH/CH_2Cl_2), followed by treatment with activated charcoal and filtration, gave 40.7 g (72%) of **14** as a yellow foam. $[\alpha]_D = -22.4$ ($c = 0.87$, EtOH). IR (thin film): 3303*m*, 2974*m*, 1749*s*, 1713*s*, 1641*s*, 1518*s*, 1497*s*, 1174*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*d*, $J = 6.8$, 3 H); 0.99 (*d*, $J = 6.8$, 3 H); 1.45 (*s*, 9 H); 2.07 (*m*, 1 H); 3.17 (*s*, 3 H); 3.79 (*m*, 2 H); 3.82 (*d*, $J = 17.2$, 1 H); 4.51 (*d*, $J = 17.3$, 1 H); 4.89 (*dd*, $J = 9.0$, 5.9, 1 H); 5.11 (br. *s*, 1 H); 5.16 (*s*, 2 H); 6.70 (br. *d*, $J = 9.2$, 1 H); 7.34 (*m*, 5 H). Signals from the minor rotamer are visible at 1.71, 2.98, and 5.19 ppm (all *s*). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.1 (*q*); 19.4 (*q*); 28.2 (*q*); 31.4 (*d*); 36.7 (*q*); 44.2 (*t*); 49.7 (*t*); 51.5 (*t*); 53.3 (*d*); 67.1 (*t*); 80.2 (*s*); 128.4 (*d*); 128.5 (*d*); 128.6 (*d*); 135.2 (*s*); 155.8 (*s*); 168.6 (*s*); 169.1 (*s*); 172.2 (*s*). FAB-MS: 458.1 (5, $[M + 23]^+$), 436.1 (65, $[MH]^+$), 380.1 (36), 201.0 (28), 180.1 (100), 173.0 (28), 129.1 (23), 90.9 (83).

Boc-Gly-Val-Sar-OH (**15**). As described for **5**, with **14** (40.5 g, 93.0 mmol), MeOH (250 ml), and 10% Pd/C (1.90 g): 32.1 g (99%) of **15** as a colorless foam. $[\alpha]_D = -7.4$ ($c = 1.0$, EtOH). IR (thin film): 3700–2400 *m*, 3309*m*, 2978*m*, 1717*s*, 1634*s*, 1500*m*, 1168*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*d*, $J = 6.7$, 3 H); 1.00 (*d*, $J = 6.7$, 3 H); 1.44 (*s*, 9 H); 2.06 (*m*, 1 H); 3.24 (*s*, 3 H); 3.60–4.30 (*m*, 4 H); 4.88 (app. *t*, $J = 8$, 1 H); 5.54 (br. *s*, 1 H); 6.90–6.50 (br. *s*, 1 H); 7.61 (br. *d*, 1 H). Signals of the minor rotamer are visible at 2.99 (*s*) and 4.67 (app. *t*). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.7 (*q*); 19.3 (*q*); 28.3 (*q*); 31.5 (*d*); 31.6 (*d*); 35.4 (*q*); 37.5 (*q*); 43.6 (*t*); 50.6 (*t*); 51.5 (*t*); 53.8 (*d*); 80.4 (*s*); 156.4 (*s*); 169.4 (*s*); 170.4 (*s*); 171.0 (*s*); 173.2 (*s*). FAB-MS: 368.1 (64, $[M + 23]^+$), 346.1 (58, $[MH]^+$), 290.0 (74), 201.0 (61), 173.1 (67), 89.9 (96), 71.9 (100).

Boc-Gly-Val-Sar-Sar-OCH$_2$Ph (**16**). As described for **14**, with sarcosine benzyl ester toluene-4-sulfonate (35.9 g, 102 mmol), **15** (31.9 g, 92.4 mmol), CH_2Cl_2 (350 ml), $Et(i\text{-}Pr)_2N$ (47.8 ml, 279 mmol), BOP-Cl (25.96 g, 102 mmol). Purification by FC (2%→3%→5% MeOH/CH_2Cl_2) gave 37.2 g (79%) of **16** as a colorless foam. $[\alpha]_D = -9.6$ ($c = 1.0$, EtOH). IR (thin film): 3309*m* (br.), 2967*m*, 1748*m*, 1712*m*, 1670*s*, 1639*s*, 1500*m*, 1173*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, $J = 6.7$, 3 H); 1.00 (*d*, $J = 6.9$, 3 H); 1.45 (*s*, 9 H); 2.10 (*m*, 1 H); 3.07 (*s*, 3 H); 3.16 (*s*, 3 H); 3.65–3.90 (*m*, 2 H); 3.89 (*d*, $J = 16.1$, 1 H); 4.02 (*d*, $J = 17.4$, 1 H); 4.34 (*d*, $J = 17.4$, 1 H); 4.62 (*d*, $J = 16.2$, 1 H); 4.92 (*dd*, $J = 9$, 6, 1 H); 5.05–5.25 (*m*, 3 H); 6.72 (*d*, $J = 9.1$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.2 (*q*); 19.6 (*q*); 28.3 (*q*); 31.4 (*d*); 35.7 (*q*); 36.7 (*q*); 49.3 (*t*); 49.6 (*t*); 51.1 (*t*); 53.4 (*d*); 67.1 (*t*); 80.2 (*s*); 128.4 (*d*); 128.5 (*d*); 128.6 (*d*); 128.8 (*d*); 135.3 (*s*); 155.8 (*s*); 168.1 (*s*); 168.8 (*s*); 169.0 (*s*); 172.2 (*s*). FAB-MS: 529.1 (24, $[M + 23]^+$), 507.1 (16, $[MH]^+$), 328.1 (26), 272.0 (52), 251.1 (100), 173.1 (26), 91.0 (55), 71.9 (69).

Boc-Gly-Val-Sar-Sar-OH (**17**). As described for **5**, with **16** (37.0 g, 73.0 mmol), MeOH (200 ml), and 10% Pd/C (2.00 g): 30.4 g (99%) of **17** as a colorless foam. $[\alpha]_D = -4.6$ ($c = 0.82$, EtOH). IR (thin film): 3600–2500 *m* (br.), 3309*m*, 2967*m*, 1712*s*, 1665*s*, 1639*s*, 1500*m*, 1406*m*, 1168*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, $J = 6.6$, 3 H); 1.00 (*d*, $J = 6.7$, 3 H); 1.44 (*s*, 9 H); 2.10 (*m*, 1 H); 3.08 (*s*, 3 H); 3.20 (*s*, 3 H); 3.60–4.60 (*m*, 6 H); 4.90 (*m*, 1 H); 5.48 (br. *s*, 1 H); 7.24 (br. *s*, 1 H); 8.20–8.80 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.4 (*q*); 19.4 (*q*); 28.3 (*q*); 31.3 (*d*); 35.8 (*q*); 37.2 (*q*); 44.0 (*t*); 49.6 (*t*); 51.1 (*t*); 53.7 (*d*); 80.0 (*s*); 156.1 (*s*); 168.3 (*s*); 169.8 (*s*); 171.4 (*s*);

172.8 (*s*). FAB-MS: 439.1 (26, $[M + 23]^+$), 417.1 (6, $[MH]^+$), 328.1 (16), 272.0 (36), 173.1 (25), 161.1 (100), 71.9 (79).

Boc-Gly-Val-Sar-Sar-OPFP (**18**) *and Gly-Val-Sar-Sar-OPFP Trifluoroacetate* (**19**). As described for **10** and **11**, with **17** (6.66 g, 15.9 mmol), pyridine (50 ml), and pentafluorophenol trifluoroacetate (5.29 g, 18.8 mmol), and 44% CF_3COOH in CH_2Cl_2. The crude **19** was dried under high vacuum overnight and cyclized to **2** immediately.

Boc-D-Ala-Sar-OCH$_2$Ph (**20**). As described for **4**, with Boc-D-alanine (22.72 g, 128 mmol), Et(i-Pr)$_2$N (43.8 ml, 256 mmol), BOP-Cl (36.0 g, 141 mmol), CH_2Cl_2 (640 ml), sarcosine benzyl ester toluene-4-sulfonate (49.69 g, 141 mmol), Et(i-Pr)$_2$N (22.4 ml, 131 mmol), and CH_2Cl_2 (500 ml). Purification by FC (hexane/AcOEt 2:1) gave 41.13 g (92%) of **20** as a pale yellow oil. $[\alpha]_D = +8.6$ ($c = 1.29$, $CHCl_3$). IR (thin film): 3426*w*, 3323*w* (br.), 2974*m*, 1748*s*, 1709*s*, 1654*s*, 1174*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25, 1.32 (2*d*, $J = 6.7$, 6.9, 3 H, rotamers); 1.42, 1.44 (2*s*, 9 H, rotamers); 2.98, 3.12 (2*s*, 3 H, rotamers); 4.16 (*ABq*, $J = 17.3$, $\nu_A = 3.93$, $\nu_B = 4.39$, 2 H); 4.68 (*m*, 1 H); 5.17, 5.20 (2*s*, 2 H); 5.44 (*d*, $J = 7.5$, 1 H); 7.35 (*s*, 5 H). ^{1}H-NMR (360 MHz, (D_6)DMSO, 170°): 1.17 (*d*, $J = 6$, 3 H); 2.57 (*s*, 9 H); 3.01 (*s*, 3 H); 4.15 (*ABq*, $J = 18$, $\nu_A = 4.11$, $\nu_B = 4.20$, 2 H); 4.45 (*m*, 1 H); 5.14 (*s*, 2 H); 5.83 (br. *s*, 1 H); 7.32 (*s*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.8 (*q*); 28.4 (*q*); 36.4 (*q*); 46.3 (*d*); 49.8 (*t*); 67.1 (*t*); 79.6 (*s*); 128.4 (*d*); 128.5 (*d*); 128.7 (*d*); 135.3 (*s*); 155.1 (*s*); 168.8 (*s*), 173.6 (*s*). FAB-MS: 373.1 (11, $[M + 23]^+$), 351.1 (35, $[M + 1]^+$), 295.0 (53), 251.1 (65), 180.1 (33), 134.0 (20), 91.0 (100).

Boc-D-Ala-Sar-OH (**21**). As described for **5**, with **20** (25.56 g, 73.0 mmol), MeOH (200 ml), and 10% Pd/C (1.28 g): 18.15 g (96%) of **21**. $[\alpha]_D = +32.0$ ($c = 0.99$, EtOH). IR (thin film): 3428*m* (br.), 2985*m*, 1703*s* (br.), 1649*s* (br.), 1216*s*, 1167*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29, 1.34 (2*d*, $J = 6.8$, 6.8, 3 H, rotamers); 1.42, 1.43 (2*s*, 9 H, rotamers); 3.00, 3.15 (2*s*, 3 H, rotamers); 4.15 (*ABq*, $J = 17.5$, $\nu_A = 3.94$, $\nu_B = 4.35$, 2 H); 4.58, 4.70 (*m*, 1 H, rotamers), 5.62, 5.69 (2*d*, $J = 8.2$, 1 H, rotamers), 7.6–8.1 (br. *s*, 1 H). ^{1}H-NMR (360 MHz, (D_6)DMSO, 170°): 1.20 (*d*, $J = 7$, 3 H); 1.38 (*s*, 9 H); 2.98 (*s*, 3 H); 4.01 (*ABq*, $J = 12$, $\nu_A = 3.95$, $\nu_B = 4.05$, 2 H); 4.43 (*m*, 1 H); 5.83 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.4 (*q*); 28.4 (*q*); 36.4 (*q*); 46.3 (*d*); 49.7 (*t*); 79.9 (*s*); 155.4 (*s*); 172.1 (*s*); 174.2 (*s*). FAB-MS: 283.1 (38, $[M + 23]^+$), 261.1 (43, $[M + 1]^+$), 205.1 (96), 161.1 (100), 90.0 (82).

Boc-D-Ala-Sar-MeLeu-OCH$_2$Ph (**22**). As described for **4**, with **21** (16.28 g, 63.0 mmol), Et(i-Pr)$_2$N (21.6 ml, 126 mmol), CH_2Cl_2 (360 ml), BOP-Cl (17.56 g, 69.0 mmol), *N*-methylleucine benzyl ester hydrochloride (18.70 g, 69.0 mmol), Et(i-Pr)$_2$N (11.9 ml, 69.0 mmol), and CH_2Cl_2 (250 ml; within 2 h): 31.55 g of **22** as a yellow oil which was not further purified.

A small sample (0.95 g) was purified using radial chromatography (4 mm, hexane/AcOEt 5:4), to give a pale yellow oil (0.726 g, 76% recovery). $[\alpha]_D = +17.0$ ($c = 1.00$, EtOH). IR (thin film): 3423*w*, 2954*m*, 1739*s*, 1708*s*, 1651*s* (br.), 1487*s*, 1405*m*, 1302*m*, 1171*s*, 753*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91, 0.94 (2*d*, $J = 6.7$, 6.5, 6 H); 0.89–0.99; further signals from rotamers; 1.23, 1.27, 1.34 (3*d*, $J = 7.1$, 6.9, 6.8, 3 H, rotamers); 1.42, 1.44 (2*s*, 9 H, rotamers; signal at 1.44 overlapping with *m* at 1.48); 1.48 (*m* overlapping with *s* at 1.44, 1 H); 1.72 (*m*, 2 H); 2.82, 2.88, 2.90 (3*s*, 3 H, rotamers); 2.96, 2.97, 3.07 (3*s*, 3 H, rotamers); 4.22 (*ABq*, $J = 16.5$, $\nu_A = 4.11$, $\nu_B = 4.34$, 2 H); 3.83–4.40; further signals from rotamers; 4.67 (*m*, 1 H); 5.14 (*m*, 2 H); 5.31 (*dd*, $J = 10.5$, 5.3, 2 H); 5.35–5.39; further signals from rotamers; 5.46 (br. *d*, $J = 8.4$, 1 H); 7.34 (*m*, 5 H). ^{1}H-NMR (360 MHz, 170°C, (D_6)DMSO): 0.89 (*d*, $J = 6$, 3 H); 0.93 (*d*, $J = 6$, 3 H); 1.18 (*d*, $J = 7$, 3 H); 1.38 (*s*, 9 H); 1.60 (*m* overlapping with *m* at 1.68, 1 H); 1.68 (*m* overlapping with *m* at 1.60 and *m* at 1.76, 1 H); 1.76 (*m* overlapping with *m* at 1.68, 1 H); 2.86 (*s*, 3 H); 2.91 (*s*, 3 H); 4.21 (*ABq*, $J = 15$, $\nu_A = 4.19$, $\nu_B = 4.23$, 2 H); 4.41 (*m*, 1 H); 4.92 (*dd*, $J = 9$, 6, 1 H); 5.13 (*s*, 2 H); 5.73 (br. *s*, 1 H); 7.32 (*s*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.9 (*q*); 21.4 (*q*); 23.1 (*q*); 25.0 (*d*); 28.4 (*q*); 30.6 (*q*); 36.0 (*q*); 37.2 (*d*); 46.4 (*d*); 49.5 (*t*); 54.8 (*d*); 66.9 (*t*); 79.5 (*s*); 128.2 (*d*); 128.3 (*d*); 128.6 (*d*); 135.6 (*d*); 155.1 (*s*); 168.5 (*s*); 171.5 (*s*); 173.3 (*s*). FAB-MS: 500.0 (49, $[M + 23]^+$), 478.1 (83, $[M + 1]^+$), 378.0 (49), 307.0 (44), 236.0 (11), 186.9 (75), 90.9 (100).

Boc-D-Ala-Sar-MeLeu-OH (**23**). As described for **5**, with **22** (39.63 g, 83.0 mmol), MeOH (400 ml), and 10% Pd/C (1.98 g): 31.79 g of **23** as a pale yellow foam which was not further purified.

A small sample of purified **22** (0.211 g, 0.44 mmol) was hydrogenated, MeOH (25 ml) and 10% Pd/C (11 mg), to give 0.168 g (98%) of a colorless, crystalline solid **23**. M.p. 121–123°. $[\alpha]_D = -5.3$ ($c = 1.02$, EtOH). IR (thin film): 3323*w*, 2959*m*, 1706*s*, 1654*s*, 1490*m*, 1170*m*, 755*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91, 0.95 (2*d*, $J = 6.7$, 6.5, 6 H); 0.97, 0.98; further signals due to rotamers, 1.24, 1.35 (2*d*, $J = 6.8$, 6.9, 3 H, rotamers); 1.41, 1.43 (*s*, 9 H, rotamers; *s* at 1.43 overlapping with *m* at 1.49); 1.49 (*m* overlapping with *s* at 1.43, 1 H); 1.75 (*m*, 2 H); 2.86, 2.91, 2.93 (3*s*, 3 H, rotamers), 2.99, 3.14 (2*s*, 3 H, rotamers); 4.22 (*ABq*, $J = 16$, $\nu_A = 3.84$, $\nu_B = 4.60$, 2 H); 4.70 (*m*, 1 H); 5.20 (*m*, 1 H); further signals at 3.48–4.54 from rotamers; 5.57, 5.66, 5.87 (3*d*, $J = 8.2$, 8.0, 1 H, rotamers). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.3 (*q*); 21.4 (*q*); 23.2 (*q*); 25.1 (*d*); 28.4 (*q*); 30.6 (*q*); 35.7 (*q*), 36.6 (*q*); 37.0 (*t*); 46.4 (*d*); 50.0 (*t*); 55.1 (*d*); 79.5 (*s*); 155.5 (*s*); 168.7 (*s*); 174.3 (*s*); 174.6 (*s*). FAB-MS: 410.2 (100, $[M + Na]^+$), 388.2 (13, $[M + 1]^+$), 332.1 (19), 288.1 (13), 217.1 (19), 187.0 (33), 146.1 (14), 100.0 (18).

Boc-D-Ala-Sar-MeLeu-Gly-OBzl (**24**). As for **4**, with **23** (31.68 g, 81.8 mmol), $Et(i\text{-}Pr)_2N$ (28.1 ml, 164 mmol), CH_2Cl_2 (400 ml), BOP-Cl (22.90 g, 89.9 mmol), glycine benzyl ester toluene-4-sulfonate (30.37 g, 0.090 mol), $Et(i\text{-}Pr)_2N$ (15.4 ml, 89.9 mmol) and CH_2Cl_2 (300 ml, over 95 min). Purification by FC (AcOEt/hexane 2:1) gave 21.97 g (50% from **21**) of **24** as a colorless foam. $[\alpha]_D = -13.1$ (*c* = 1.11, EtOH). IR (thin film): 3323*m* (br.), 2958*m*, 1749*s*, 1654*s*, 1174*s*, 1062*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, *J* = 6.5, 3 H); 0.94 (*d*, *J* = 6.6, 3 H); 1.19, 1.34 (2*d*, *J* = 6.9, 6.9, 3 H, rotamers); 1.38, 1.44 (2*s*, 9 H, rotamers; *s* at 1.44 overlapping with *m* at 1.44); 1.44 (*m*, overlapping with *s* at 1.44, 1 H); 1.60 (*m*, 1 H); 1.79 (*m*, 1 H); 2.79, 2.82, 2.86, 2.88 (4*s*, 3 H, rotamers); 3.14, 3.16, 3.25, 3.27 (4*s*, 3 H, rotamers); 3.75–4.44 (*m*, 4 H, rotamers); 4.68 (*m*, 1 H); 5.15 (*m*, 2 H); 5.40 (*d*, *J* = 8.3, 1 H); 6.71, 6.80, 7.00 (3*m*, 1 H, rotamers); 7.30–7.39 (*m*, 5 H). ^{1}H-NMR (360 MHz, (D_6)DMSO, 170°): 0.87 (*d*, *J* = 6, 3 H); 0.91 (*d*, *J* = 6, 3 H); 1.20 (*d*, *J* = 7, 3 H); 1.38 (*s*, 9 H); 1.54 (*m*, 2 H); 1.75 (*m*, 1 H); 2.83 (*s*, 3 H); 2.95 (*s*, 3 H); 3.90 (*dd*, *J* = 6, 2, 2 H); 4.21 (*m*, 2 H); 4.42 (*m*, 1 H); 4.84 (br. *s*, 1 H); 5.13 (*s*, 2 H); 5.81 (br. *s*, 1 H); 7.31 (*m*, 5 H); 7.52 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.6 (*q*); 21.9 (*q*); 23.0 (*q*); 24.9 (*d*); 28.4 (*q*); 30.1 (*q*); 35.8 (*t*); 36.8 (*q*); 41.3 (*t*); 46.4 (*d*); 50.0 (*t*); 54.7 (*d*); 67.1 (*t*); 79.6 (*s*); 128.4 (*d*); 128.6 (*d*); 135.27 (*s*); 155.1 (*s*); 168.6 (*s*); 169.3 (*s*); 170.8 (*s*); 173.7 (*s*). FAB-MS: 557.1 (10, $[M + 23]^+$), 535.1 (10, $[M + 1]^+$), 435.1 (35), 370.1 (21), 314.0 (74), 293.1 (37), 187.0 (100), 143.0 (37), 100.0 (94), 90.9 (88).

Boc-D-Ala-Sar-MeLeu-Gly-OH (**25**). As described for **5**, with **24** (9.92 g, 18.6 mmol), MeOH (150 ml), and 10% Pd/C (0.50 g): 8.34 g (99%) of **25** as a colorless foam. $[\alpha]_D = -12.5$ (*c* = 1.23, EtOH). IR (thin film): 3326*w*, 2960*m*, 1653*s*, 1522*m*, 1405*m*, 1368*m*, 1170*m*, 1063*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*d*, *J* = 6.5, 3 H); 0.96 (*d*, *J* = 6.6, 3 H); 1.30, 1.35 (2*d*, *J* = 6.6, 6.9, 3 H, rotamers); 1.41. 1.42 (2*s*, 9 H, rotamers); 1.61 (*m*, 2 H); 1.79 (*m*, 1 H); 2.92, 2.93, 2.96, 2.97 (4*s*, 3 H, rotamers); 3.14, 3.18, 3.27 (4*s*, 3 H, rotamers); 3.71–4.46 (*m*, 4 H, rotamers); 4.66 (*m*, 1 H); 5.23 (*m*, 1 H); 5.54, 5.65 (2*d*, *J* = 8.1, 8.3, rotamers); 6.93 (*m*, H). ^{1}H-NMR (360 MHz, 170°C, (D_6)DMSO): 0.93 (*d*, *J* = 6, 3 H); 0.96 (*d*, *J* = 6, 3 H); 1.24 (*d*, *J* = 7, 3 H); 1.43 (*s*, 9 H); 1.60 (*m*, 2 H); 1.79 (*m*, 1 H); 2.90 (*s*, 3 H); 3.01 (*s*, 3 H); 3.82 (*m*, 2 H); 4.27 (*s*, 2 H); 4.47 (*m*, 1 H); 4.88 (br. *s*, 1 H); 5.86 (br. *s*, 1 H); 7.37 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.9 (*q*); 21.9 (*q*); 23.0 (*q*); 24.9 (*d*); 28.3 (*q*); 30.1 (*q*); 36.0 (*t*); 36.9 (*q*); 41.1 (*t*); 46.4 (*d*); 50.2 (*t*); 54.8 (*d*); 79.9 (*s*); 155.4 (*s*); 169.3 (*s*); 170.7 (*s*); 171.9 (*s*); 174.7 (*s*). FAB-MS: 467.3 (19, $[M + Na]^+$), 445.3 (3, $[M + 1]^+$), 345.2 (15), 314.2 (32), 203.2 (22), 187.1 (62), 132.9 (100), 100.0 (56).

Boc-D-Ala-Sar-MeLeu-Gly-OPFP (**26**) *and D-Ala-Sar-MeLeu-Gly-OPFP Trifluoroacetate* (**27**). As described for **10** and **11**, with **25** (5.80 g, 13.0 mmol), pyridine (50 ml), and pentafluorophenyl trifluoroacetate (4.37 g, 15.6 mmol), and 44% CF_3COOH in CH_2Cl_2. The crude **27** was dried under high vacuum overnight and cyclized to **3** immediately.

3. *Cyclization of* **11**, **19**, *and* **27**. *Cyclo(-Leu-Sar-Sar-Gly-)* (**1**). In two 10-l round-bottomed three-necked flasks, fitted with condensers, overhead stirrers, and precision addition funnels, a soln. of dioxane (10.56 l), pyridine (3.2 l), CF_3CH_2OH (240 ml), and 4-(dimethylamino)pyridine (DMAP, 1.56 g, 12.8 mmol) was heated to between 90–100°. A soln. of **11** (9.77 g, 16.0 mmol from **10**) in dioxane (2 l) was added dropwise (rate 1 drop/s), with continuous fast stirring and heating over 24 h. After the addition was complete, the soln. was heated for 2 h, cooled to r.t., and concentrated. The resulting crude brown residue was filtered through basic *Dowex* in MeOH, concentrated, filtered through acidic *Dowex* in MeOH, and concentrated. Purification by FC (2%→4%→7% $MeOH/CH_2Cl_2$), followed by purification by prep. HPLC (RP-C_{18}, 100% H_2O 5 min.→50% H_2O/CH_3CN 55 min), gave 2.09 g (42%) of **1** as a colorless powder. M.p. 180–185° (subl., sealed tube). Heating a sample, of **1** in an open m.p. tube gives an undefined m.p. (*ca.* 160–180°). Samples used for analysis and alkylations were recrystallized from i-PrOH, followed by lyophilization to remove trace amounts of the solvent. $[\alpha]_D = -12.7$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3700–3000*m* (br.), 3290*m*, 2958*m*, 1660*s* (br.), 1540*w*, 1401*w*, 1256*w*, 1091*w*. ^{1}H- and ^{13}C-NMR assignments are based on HETCOR and DNOE results (see *Fig. 6*). ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.85 (app. *t*, *J* = 6.3, 2 CH_3–C(14)); 1.40 (*m*, 3 H, 2 H–C(13) + H–C(14)); 2.73 (*s*, CH_3–N(7)); 2.89 (*s*, CH_3–N(4)); 2.92 (*d*, *J* = 14, H_i–C(8)); overlapping *s* at 2.89; 3.35 (*dd*, *J* = 19, 6.9, H_o–C(11)) overlapping H_2O signal at 3.33 ppm; 3.64 (*dd*, *J* = 17.5, 8.5, H_i–C(11)); 3.94 (*d*, *J* = 17.8, H_o–C(5)); 4.20 (*d*, *J* = 17.8, H_i–C(5)); 4.66 (*m*, H_i–C(2)); 5.08 (*d*, *J* = 13.9, H_i–C(8)); 7.68 (app. *t*, *J* = 7.2, H–N(10)); 8.06 (*d*, *J* = 9.9, H–N(1)). Integration of the N–H protons of the second (minor) conformer – visible at 6.95 and 7.85 ppm – indicating a ratio of 8.5:1 for the two conformers. ^{1}H-NMR of **1** in (D_8)THF indicated a ratio of the two conformers as 7.8:1, and in $CDCl_3$ 4.3:1. ^{13}C-NMR (100 MHz, (D_6)DMSO): 21.9 (*q*, CH_3–C(14)); 23.4 (*q*, CH_3–C(14)); 23.6 (*d*, C(14)); 35.9 (*q*, C(7)); 38.8 (*q*, C(4)); 40.6 (*t*, C(13)); 43.2 (*t*, C(12)); 46.6 (*d*, C(2)); 49.4 (*t*, C(8)); 50.1 (*t*, C(5)); 167.3 (*s*); 167.7 (*s*); 170.4 (*s*); 170.7 (*s*). FAB-MS: 335.1 (22, $[M + 23]^+$), 313.1 (69, $[M + 1]^+$), 312.1 (12), 311.1 (14), 285.1 (9), 200.1 (13), 143.1 (27), 86.0 (100). Determination of H_2O content according to the method of *Karl Fischer:* 4.1%. Anal. calc. for $C_{14}H_{25.42}N_4O_{4.71}$: C 51.71, H 7.88, N 17.23; found: C 52.02, H 7.90, N 17.53. Note: we found that the H_2O content of **1** varies greatly depending on the method of purification (*e.g.*, a sample of **1** obtained by sublimation, 180–190° at 2×10^{-5} bar, contained 1.39% H_2O).

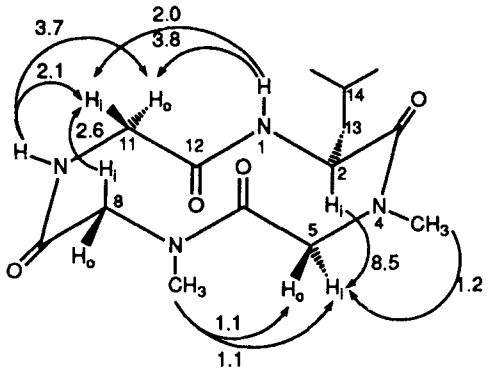

Fig. 6. *DNOE* (300 MHz, (D_6)DMSO) *Results for* **1**. Enhancements are given in %. For clarity, those enhancements less than 1%, and of geminal sustituents, are not shown.

Cyclo(-Val-Sar-Sar-Gly-) (**2**). As described for **1**, with dioxane (12.1 l), pyridine (1.8 l), 2,2,2-trifluoroethanol (270 ml), DMAP (1.27 g, 10.4 mmol), **19** (4.77 g, 8.00 mmol), dioxane (2 l). Purification by FC (10% MeOH/CH_2Cl_2), followed by prep. HPLC (*RP-C*$_8$, 5% MeCN/H_2O), gave 0.419 g (18%) of **2** as colorless solid. M.p. 217–219° (dec., sealed tube). $[\alpha]_D = +36.8$ ($c = 0.99$, EtOH). IR (KBr): 3700–3000*m* (br.), 2960*m*, 2930*m*, 2880*w*, 1660*s* (br.), 1450*s*, 1400*s*, 1255*w*, 1185*w*, 1090*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.78 (*d*, $J = 6.8$, CH_3–C(13)); 0.84 (*d*, $J = 6.5$, CH_3–C(13)); 2.01 (*m*, H–C(13)); 2.73 (*s*, CH_3–N(7)); 2.90 (*s*, CH_3–N(4)); overlapping *d* at 2.92; 2.92 (*d*, $J = 13$, H_o–C(8)); 3.38 (*dd*, $J = 17.7, 6.7$, H_o–C(11)); 3.70 (*dd*, $J = 17.9, 8.5$, H_i–C(11)); 3.93 (*d*, $J = 17.7$, H_o–C(5)); 4.21 (*d*, $J = 17.9$, H_i–C(5)); 4.29 (app. *t*, $J = 9.2$, H_i–C(2)); 5.08 (*d*, $J = 13.9$, H_i–C(8)); 7.68 (app. *t*, $J = 7.2$, H–N(10)); 8.02 (*d*, $J = 9.9$, H–N(1)). ^{13}C-NMR (100 MHz, (D_6)DMSO): 18.0 (*q*); 20.2 (*q*); 28.9 (*d*); 32.9 (*q*); 35.7 (*q*); 43.1 (*t*); 49.3 (*t*); 49.9 (*t*); 53.8 (*d*); 167.6 (*s*); 167.9 (*s*); 169.7 (*s*); 170.6 (*s*). As for (D_6)DMSO, ^{1}H-NMR in CD_3OD showed only one conformer. ^{1}H-NMR in $CDCl_3$ (300 MHz) indicated a *ca.* 1:1 ratio of conformers. ^{1}H-NMR in $CDCl_3$ at 50° (300 MHz) showed a broadening of the signals for one of the conformers. ^{1}H-NMR in (D_8)THF (200 and 300 MHz) indicated the presence of only one conformer, by all appearance identical with that in DMSO (see *Fig. 9*). FAB-MS: 321.1 (4, $[M + 23]^+$), 299.1 (100, $[M + 1]^+$), 289.0 (12), 200.1 (11), 136.0 (73), 120.0 (15), 107.0 (28), 88.9 (25).

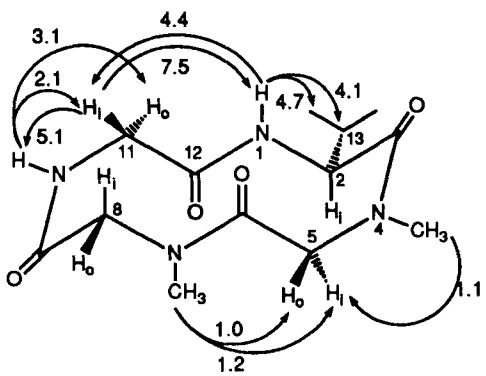

Fig. 7. *DNOE* (300 MHz, (D_6)DMSO) *Results for* **2**

Cyclo(-D-Ala-Sar-MeLeu-Gly-) (**3**). As described for **1**, with dioxane (12.1 l), pyridine (1.8 l), 2,2,2-trifluoroethanol (270 ml), DMAP (1.27 g, 10.4 mmol), **27** (9.29 g, 13.0 mmol), dioxane (2 l). Purification by recrystallizing twice from EtOH/hexane gave 1.29 g (30% from **25**) of **3** as a colorless solid. An anal. sample was prepared by recrystallization from EtOH and drying under vacuum at 135°. M.p. 262–263°. $[\alpha]_D = -14.6$ ($c = 0.98$, H_2O). IR

(KBr): 3700–3100*m* (br.), 3420*m* (br.), 3280*m*, 3100*w*, 2950*m*, 1660*s*, 1550*m*, 1460*m*, 1400*m*, 1090*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (app. *t*, *J* = 6, 2 CH_3–C(14)); 1.29 (*d*, *J* = 6.7, CH_3–C(8)); 1.51 (*m*, 2 H, 2 H–C(13)); 1.74 (*m*, 1 H, H–C(14)); 2.71 (*s*, CH_3–N(1)); 3.09 (*s*, CH_3–N(10)); 3.60 (*dd*, *J* = 17.5, 6.5, H_o–C(5)); 3.62 (*d*, *J* = 17.8, H_o–C(11)); 3.90 (*dd*, *J* = 17.5, 6.5, H_o–C(5)); 4.89 (*m*, H_i–C(8)); 5.28 (*dd*, *J* = 8.0, 6.1, H_i–C(2)); 5.90 (br. *d*, *J* = 10.2, H–N(7)); 6.13 (br. *m*, H–N(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.6 (*q*); 22.6 (*q*); 23.0 (*q*); 24.5 (*d*); 29.3 (*q*); 36.6 (*t*); 36.8 (*q*); 43.8 (*t*); 45.7 (*d*); 50.9 (*q*); 51.3 (*d*); 166.9 (*s*); 168.5 (*s*); 170.6 (*s*); 171.9 (*s*). Only one conformer of **3** was observed in all NMR solvents. FAB-MS: 349.2 (20, $[M + 23]^+$), 327.2 (100, $[M + 1]^+$), 256.1 (7), 200.1 (10), 154.0 (43), 137.0 (38), 100.0 (37). Anal. calc. for $C_{15}H_{26}N_4O_4$: C 55.20, H 8.03, N 17.17; found: C 54.84, H 8.22, N 17.07.

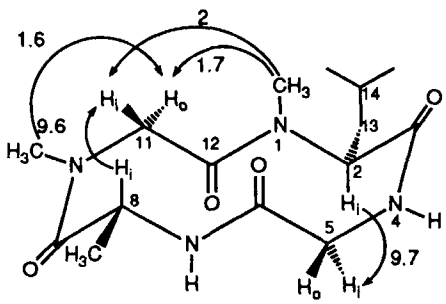

Fig. 8. *DNOE* (300 MHz, $CDCl_3$) *Results for* **3**

4. *Solubility Studies of* **1**–**3** *in THF in the Absence and Presence of LiBr. Solubility of* **1** *in the Absence of LiBr.* To **1** (0.100 g, 0.32 mmol) was added THF (2 ml). After 1 h, an additional 4 ml of THF was added and the heterogeneous soln. stirred overnight. The mixture was removed with a syringe, fitted with a membrane filter, and 5 ml were concentrated and dried: 0.066 g, corresponding to a solubility of 0.013 g/ml.

Solubility of **1** *in the Presence of LiBr. a*) To LiBr (0.0307 g, 0.353 mmol) and **1** (0.055 g, 0.176 mmol) was added THF in 0.2- to –1.0 ml increments, stirring 15 min between additions, until the soln. became homogeneous: 5.5 ml of THF added, 0.010 g/ml. The resulting soln. was concentrated and dried under vacuum for 5 h to give a colorless foam (0.214 g) which was redissolved in 3.84 ml of THF. Thus, the solubility range of **1** in the presence of 2 equiv. of LiBr is 0.010–0.014 g/ml). *b*) Repeating this procedure with LiBr (0.0516 g, 0.594 mmol) and **1** (0.0464 g, 0.148 mmol), the soln. became homogeneous within 10 min after the addition of 0.5 ml of THF. After concentrating and drying, the resulting colorless foam (0.223 g) was redissolved in 0.14 ml of THF for a solubility range of 0.093–0.166 g/ml. *c*) Similarly, LiBr (0.0981 g, 1.13 mmol) and **1** (0.0588 g, 0.148 mmol) resulted in a solubility range of 0.084–0.113 g/ml.

Solubility of **2**. As described for **1**, with **2** (0.0485 g, 0.162 mmol). Concentration of 3 ml of filtered soln. gave 0.0294 g for a solubility of 0.0098 g/ml. *a*) LiBr (0.0157 g, 0.181 mmol), **2** (0.0252 g, 0.085 mmol), and THF (6.4 ml): 0.0039 g/ml. *b*) LiBr (0.0276 g, 0.32 mmol), **2** (0.0239 g, 0.080 mmol), and THF (17 ml): 0.0014 g/ml. *c*) LiBr (0.0661 g, 0.761 mmol), **2** (0.0370 g, 0.124 mmol), and THF (28 ml): 0.0013 g/ml.

The solubilities at –78° were determined as described above, except that the solid peptide and LiBr were cooled to –78° prior to the addition of THF: *a*) LiBr (0.0122 g, 0.14 mmol), **2** (0.019 g, 0.064 mmol), and THF (8.8 ml): 0.0022 g/ml. *b*) LiBr (0.0276 g, 0.32 mmol), **2** (0.0239 g, 0.080 mmol), and THF (3.0 ml): 0.0080 g/ml. *c*) LiBr (0.0646 g, 0.744 mmol), **2** (0.0368 g, 0.123 mmol), and THF (7 ml): 0.0052 g/ml.

An NMR sample of **2** was prepared by placing 0.005 g (0.0168 mmol) in an oven-dried NMR tube and cooling to –78° under Ar. Addition of a 0.35M soln. of LiBr in (D_8)THF (0.6 ml, 0.209 mmol) to the peptide resulted in a clear supernatant soln. with some residual, undissolved, peptide. This sample was then analyzed by ^{1}H-NMR (300 MHz) at –78°, –30° and r.t. (the soln. became turbid upon warming to r.t., see *Fig. 9*).

Solubility of **3**. As described for **1**, with **3** (0.052 g, 0.159 mmol). Filtering and concentrating 3 ml gave 0.0126 g, which was redissolved in 1.2 ml of THF: 0.0042–0.0105 g/ml, *a*) LiBr (0.010 g, 0.115 mmol), **3** (0.0188 g, 0.058 mmol), and THF (9.5 ml). Concentrating gave 0.0301 g, which redissolved in 7.3 ml of THF: 0.0020–0.0026 mg/ml. *b*) LiBr (0.0224 g, 0.258 mmol), **3** (0.0210 g, 0.064 mmol), and THF (13.8 ml). After concentrating, the dry residue was redissolved in 13 ml of THF: 1.52–1.62 mg/ml. *c*) LiBr (0.0456 g, 0.525 mmol), **3** (0.0286 g, 0.088 mmol), and THF (18.6 ml). After concentrating, the dry residue was redissolved in 17.8 ml of THF: 1.54–1.61 mg/ml.

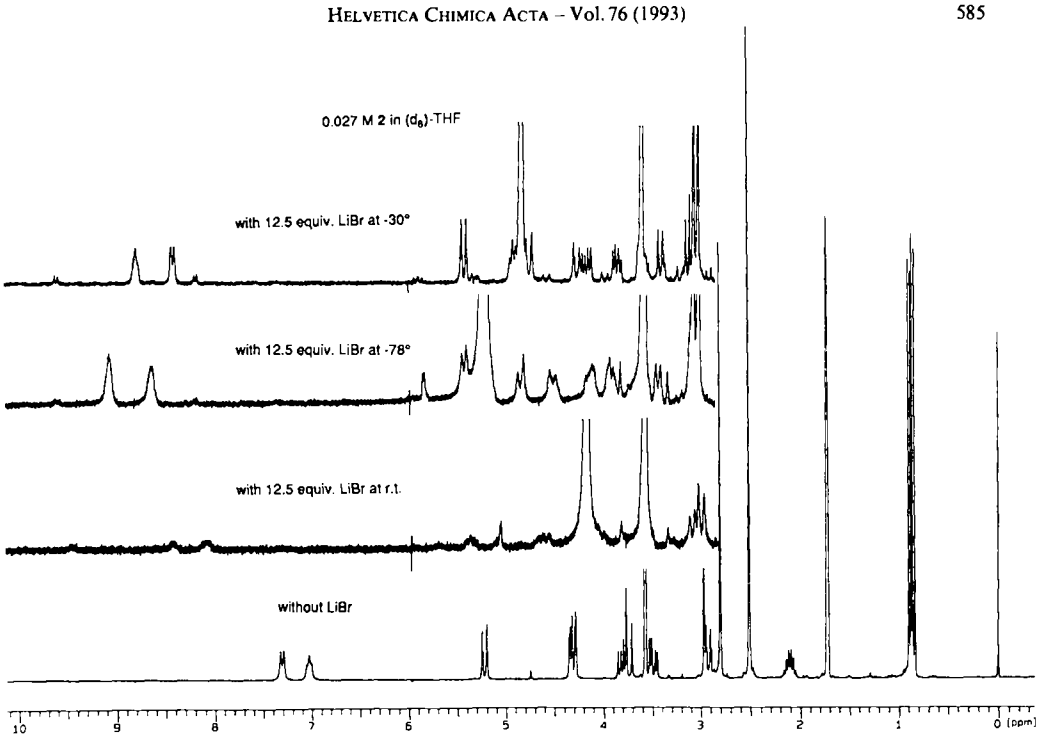

Fig. 9. *^{1}H-NMR* (300 MHz, (D_8)THF) *Spectra of* **2**

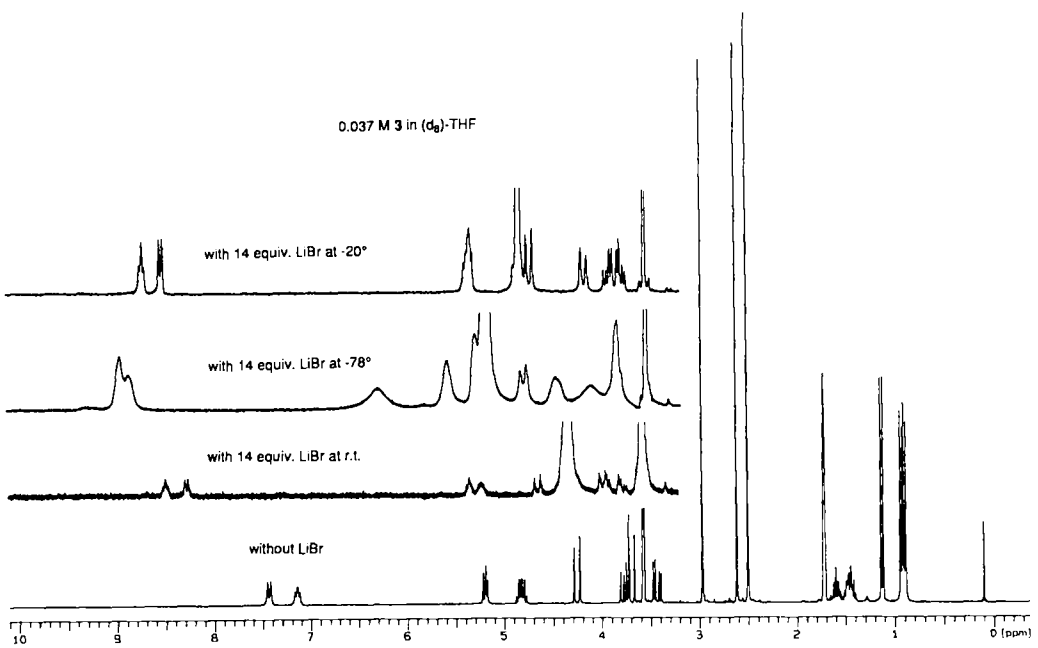

Fig. 10. *^{1}H-NMR* (300 MHz, (D_8)THF) *Spectra of* **3**

Solubility at −78°. **3** (0.010 g, 0.031 mmol) was 'titrated' with THF while stirring. After 5 ml of THF had been added, there had been no noticeable solubilization (the peptide remained in clumps): < 2.0 mg/ml. *a*) LiBr (0.0103 g, 0.119 mmol), **3** (0.0193 g, 0.059 mmol), and THF (2.3 ml): 0.0084 g/ml. *b*) LiBr (0.0227 g, 0.261 mmol), **3** (0.0213 g, 0.065 mmol), and THF (2.4 ml): 0.0089 g/ml. *c*) LiBr (0.0393 g, 0.452 mmol), **3** (0.0246 g, 0.075 mmol), and THF (3.0 ml): 0.0082 g/ml.

An NMR sample of **3** was prepared as described for **2**, with 0.006 g (0.0184 mmol) and 0.51M LiBr in (D_8)THF (0.50 ml, 0.257 mmol), resulting in a clear soln., without any undissolved peptide visible. This sample was analyzed by ^{1}H-NMR at −78° and −20° at which point peptide began to precipitate out of soln. Another NMR soln. of **3** was prepared at r.t., giving a turbid soln., ^{1}H-NMR of which shows very little peptide dissolved (see *Fig. 10*).

5. *Alkylation of the Cyclic Peptides: General Procedure.* Unless otherwise stated, the following procedure was applied: A stock soln. of 0.40M LDA in THF was prepared at −78° as described in [14]. Separately, a soln. of the peptide was prepared by adding the LiBr/THF soln. to the peptide at r.t. (for **1**), or at −78° (for **2** and **3**), followed by THF and DMPU (DMPU was not employed in the alkylations of **2**, due to separation difficulties). After stirring for 30 min, the LDA soln. was added to the peptide *via* syringe (LDA soln. at 0°), or cannula (LDA soln. at −78°), and the resulting clear/colorless-pale yellow soln. stirred at −78° for 2 h. After addition of the electrophile, the reaction soln. was stirred overnight. Unless otherwise stated, the following workup procedure was used: To the reaction soln. was added a 10% AcOH soln. in THF (1.1 equiv.) and the resulting heterogeneous soln. warmed to r.t. and concentrated. Following analysis by anal. HPLC (for the alkylation of **1** and **2**: *RP-*C_8, for **3**: *RP-*C_4), the crude mixture was purified by prep. HPLC. Unless otherwise stated, for reaction mixtures from **3**, the crude residue (usually a colorless foam) was dissolved in MeOH and treated with basic and then acidic *Dowex*. After removal of the MeOH the sample was then purified by HPLC. Generally, poor resolution was obtained on attempted prep. HPLC purification of reaction mixtures from **3**, when not treated with *Dowex*.

*Cyclo(-Leu-*L*-(D_1)Sar-Sar-Gly-)* (**28a**). To **1** (0.100 g, 0.320 mmol) was added LiBr (0.111 g, 1.28 mmol) followed by THF (5 ml). After stirring for 1 h at r.t., DMPU (0.154 ml, 1.28 mmol) was added, the soln. was cooled to −78°, and LDA (4 ml, 2.08 mmol) was added *via* a cannula, followed by 0.5 ml of THF. After 1.5 h at −78°, BuLi (0.73 ml, 1.09 mmol) was introduced. After additional 10 min, CF_3CO_2D (0.34 ml, 4.48 mmol, in 1 ml THF) was added. The resulting heterogeneous soln. was warmed to r.t., concentrated, and treated, in succession, with basic and acidic *Dowex* in MeOH. After concentrating, the sample was purified by prep. HPLC (*RP-*C_8, 10% MeCN/H_2O) to give 0.064 g (64%) of a colorless solid. $[\alpha]_D = -13.1$ ($c = 1.03$, $CHCl_3$). Except as noted, spectral data are identical with those of **1**. ^{1}H-NMR (400 MHz, (D_6)DMSO) showed a decrease in the signal at 3.94 ppm (*d*, $J = 17.8$, H_o–C(5)) and the signal at 4.20 ppm H_i–C(5)) collapsing to a *s*. Integration, difficult due to the presence of signals resulting from the minor conformer, indicated at 65% D incorporation. ^{13}C-NMR (100 MHz, (D_6)DMSO) showed a decrease in the intensity of the *t* at 50.1 ppm and the appearance of a D-coupled signal. ^{1}H-NMR (46 MHz, DMSO): 3.90 (br. *s*). FAB-MS: 627.1 (13, $[2M + 1]^+$), 336.1 (39, $[M + 23]^+$), 314.1 (100, $[M + 1]^+$), 86.0 (6).

*Cyclo(-Leu-Me-*LD*-Ala-Sar-Gly-)* (**28b**/**29b**) *and Cyclo(-Leu-Me-*L*-Ala-Sar-Sar-)* (**30b**). *With 10 equiv. of LHMDS and 6 equiv. of DMPU.* With **1** (0.025 g, 0.0080 mmol), LiBr/THF (0.23 ml, 0.160 mmol), THF (2.77 ml), DMPU (0.058 ml, 0.480 mmol), LHDMS – prepared as described for LDA – (2.0 ml, 0.080 mmol), and MeI (0.06 ml, 0.96 mmol, added after 2.5 h.). The reaction was quenched with AcOH (0.05 ml, 0.834 mmol, in 0.1 ml THF). Purification by prep. HPLC (8% MeCN/H_2O) gave 0.0091 g (36%) of recovered **1**, and 0.0105 g (40%) of **28b**.

With 10 equiv. of LDA and 4 equiv. of DMPU. With **1** (0.025 g, 0.0080 mmol), LiBr/THF (0.23 ml, 0.160 mmol), THF (2.73 ml), DMPU (0.038 ml, 0.320 mmol), LDA (2.0 ml, 0.800 mmol), MeI (0.060 ml, 0.960 mmol). The color of the soln. changed from pale yellow to colorless upon addition of the MeI. After quenching with AcOH (0.05 ml, 0.834 mmol, in 0.1 ml THF) and concentrating, anal. HPLC (*RP-*C_8, 5% MeCN/H_2O, 1 ml/min) indicated a ratio for **28b**/**29b** of 2.0:1 (retention times for **1**:**28b**:**29b** are 27.8, 36.5, and 55.5 min., resp., with **30b** eluting, upon increasing to 12% MeCN/H_2O, after *ca.* 60 min). Purification by prep. HPLC gave **1** (0.0055 g, 22%), **28b** (0.0126 g, 48%), **29b** (0.0016 g, 6%), and **30b** (0.0017 g, 6%). Combined yield: 60%.

With 10 equiv. of LDA and 8 equiv. of DMPU. With **1** (0.025 g, 0.0080 mmol), LiBr/THF (0.23 ml, 0.160 mmol), THF (2.69 ml), DMPU (0.077 ml, 0.640 mmol), LDA (2.0 ml, 0.800 mmol), MeI (0.060 ml, 0.960 mmol). No noticeable change in the slightly turbid soln. upon addition of MeI. After quenching with AcOH (0.05 ml, 0.834 mmol, in 0.1 ml THF) and concentrating, anal. HPLC (*RP-*C_8, 5% MeCN/H_2O, 1 ml/min) indicated a ratio for **28b**/**29b** of 2.5:1. Purification by prep. HPLC gave **1** (0.0064 g, 26%), **28b** (0.0126, 48%), **29b** (0.0020 g, 8%), and **30b** (0.0029 g, 11%). Combined yield: 66%.

*Cyclo(-Leu-Me-*L*-Ala-Sar-Gly-)* (**28b**). Hydrolysis of 3 mg of **28b** with HCl, followed by derivatization with isopropyl isocyanate and GC [14] confirms the newly formed amino acid to be L-Me-alanine. Recrystallization

from AcOEt gave colorless needles, which became opaque upon drying under vacuum. M.p. 167.5–169°. $[\alpha]_D = -259.8$ ($c = 0.54$, $CHCl_3$); $[\alpha]_D = -105.6$ ($c = 0.87$, MeOH). IR (KBr): 3700–3100*m* (br.), 3295*m*, 2960*m*, 1665*s*, 1529*m*, 1399*m*, 1090*w*, 735*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.6$, 1 H); 1.01 (*d*, $J = 6.7$, 3 H); 1.20 (*ddd*, $J = 14.2, 9.8, 2.2$, 1 H); 1.42 (*d*, $J = 6.6$, CH_3–C(8)); 1.58 (*ddd*, $J = 14.5, 11.2, 3.8$, 1 H); 1.95 (*m*, 1 H); 3.02 (*s*, 3 H); 3.05 (*s*, 3 H); 3.33 (*d*, $J = 15.1$, H_o–C(2)); 3.46 (*q*, $J = 6.6$, H_i–C(8)); 3.71 (*d*, $J = 18.3$, H_o–C(11)); 3.85 (*d*, $J = 18.2$, H_i–C(11)); 3.90 (*m*, H_i–C(5)); overlapping *d* at 3.85 ppm; 4.80 (*dd*, $J = 15.1, 9.7$, H_i–C(2)); 7.81 (*d*, $J = 9.6$, H–N(1)); 8.71 (*d*, $J = 8.0$, H–N(4)). Decoupling (200 MHz) the N–H *d* at 8.71 ppm caused the *m* at 3.90 to collapse to a *dd*($J = 9, 2$), decoupling the N–H *d* at 7.81 caused the *dd* at 4.80 to collapse to a *d*($J = 15.2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.9 (*q*); 21.1 (*q*); 23.2 (*q*); 24.5 (*d*); 36.1 (*q*); 37.5 (*q*); 39.8 (*t*); 42.9 (*t*); 52.1 (*d*); 54.9 (*t*); 59.8 (*d*); 167.4 (*s*); 170.5 (*s*); 171.5 (*s*); 173.2 (*s*). In (D_6)DMSO, ^{1}H-NMR (400 MHz) indicated that **28b** exists as a mixture of three conformers, based on the presence of three Me *d*'s at 1.04 ($J = 6.6$), 1.22 ($J = 6.6$), and 1.38 ($J = 7.0$) in a *ca.* 1.1:1:1.2 ratio, resp. (integration of the *d* at 1.38 is difficult, since it overlaps with other signals). Similarly, in CD_3OD (200 MHz) three conformers are visible in a ratio of *ca.* 1:2:1.3. FAB-MS: 653.1 (13, $[2M + 1]^+$), 349.0 (18, $[M + 23]^+$), 327.0 (100, $[M + 1]^+$), 86.0 (29).

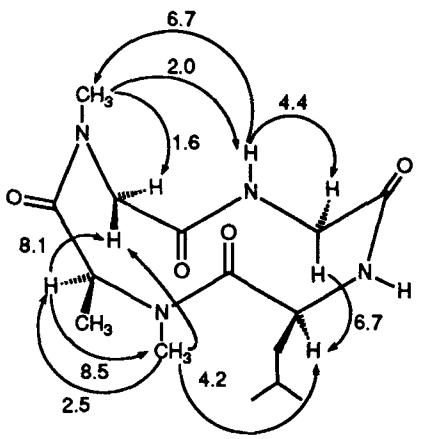

Fig. 11. *DNOE* (300 MHz, $CDCl_3$)) *Results for* **28b**

X-Ray Analysis of **28b**. Cyclo(-Leu-MeAla-Sar-Gly-) was crystallized from AcOEt as colorless platelets. The X-ray crystal structure analysis was performed by *Volker Gramlich* and *Stefano Leoni*, at ETH-Zürich. *Crystal Data:* $C_{15}H_{26}N_4O_4 \cdot C_4H_8O_2$; formula weight 326.39 + 88.11 = 414.50; $a = 9.768(5)$, $b = 14.434(5)$, $c = 16.016(6)$ Å; $\beta = 90°$; space group $P2_12_12_1$; $V = 2258.1$ Å^3; $Z = 4$; MoK_α radiation, $\lambda = 0.71073$ Å, 2θ range 3.0 to 45°; 1717 reflections collected; 1210 [$I > 4.0\sigma(I)$] observed reflections; final value of $R = 7.01\%$.

Further details concerning the crystal structure analysis may be obtained from the director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EW England, by indicating the full reference of this paper.

*Cyclo(-Leu-Me-*D*-Ala-Sar-Gly-)* (**29b**). The absolute configuration of the newly formed amino acid was determined by hydrolysis, derivatization, and GC [14]. Colorless solid. M.p. 143–145° (this m.p. reflects the incorporation of solvent in the crystal – see the m.p. for 'authenthic' **29b** below). $[\alpha]_D = -42.4$ ($c = 0.30$, $CHCl_3$). IR (KBr): 3650–3000*m* (br.), 3280*m*, 3090*w*, 2955*m*, 1660*s*, 1546*m*, 1467*m* (br.), 1402*m*, 1292*w*, 1090*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.97 (app. *t*, $J = 6.6$, 2 CH_3–C(14)); 1.23 (*d*, $J = 6.6$, CH_3–C(8)); overlapping *m* at 1.26; 1.26 (*m*, H–C(13)); 1.65 (*m*, H–C(13)), overlapped by H_2O signal; 1.98 (*m*, 1 H, H–C(14)); 2.75 (*s*, CH_3–N(1)); 3.16 (*s*, CH_3–N(4)); 3.26 (*d*, $J = 14.3$, H_o–C(2)); 3.66 (*d*, $J = 17.6$, H_o–C(11)); 4.09 (*m*, H_i–C(5)); 4.16 (*d*, $J = 17.6$, H_i–C(11)); 4.78 (*dd*, $J = 14.3, 9.6$, H_i–C(2)); 5.46 (*q*, $J = 6.7$, H_i–C(8)); 7.61 (*d*, $J = 9.6$, H–N(4)); 9.08 (*d*, $J = 8.1$, H–N(1)). With the exception of minor chemical shift differences, the ^{1}H-NMR spectrum (400 MHz, (D_6)DMSO) was identical with the spectrum in $CDCl_3$. Irradiation of the *dd* at 4.78 ppm (4.62 in DMSO) cause the *d* at 9.08 to collapse to a *s*. Irradiation of the *d* at 3.26 caused the *dd* at 4.78 to collapse to a *d*. ^{13}C-NMR (100 MHz, $CDCl_3$): 13.8 (*q*); 20.8 (*q*); 23.3 (*q*); 24.6 (*d*); 30.0 (*q*); 37.4 (*q*); 40.2 (*t*); 42.6 (*t*); 50.1 (*d*); 51.3 (*t*); 52.1 (*d*); 166.8

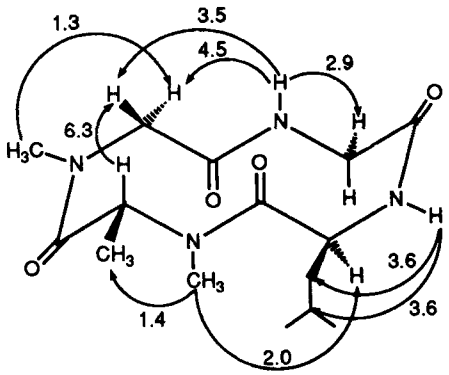

Fig. 12. *DNOE* (300 MHz, (D_6)DMSO) *Results for* **29b**

(*s*); 170.3 (*s*); 172.5 (*s*); 172.6 (*s*). FAB-MS: 653.4 (6, $[2M + 1]^+$), 349.2 (11, $[M + 23]^+$), 327.2 (62, $[M + 1]^+$), 137.1 (71).

*Cyclo(-Leu-Me-*L*-Ala-Sar-Sar-)* (**30b**). The absolute configuration of the newly formed amino acid was determined by hydrolysis, derivatization, and GC [14]. Colorless 'waxy' solid. M.p. 104–106° (may also complex solvent). $[\alpha]_D = -126.6$ ($c = 0.30$, $CHCl_3$). IR (KBr): 3700–3100*w* (br.), 2954 *m*, 1659*s*, 1527*w*, 1455*m*, 1390*m*, 1092*w*, 754*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (2*d*, $J = 6.6$, 6 H); 1.33 (*ddd*, $J = 15.0$, 10.8, 2.5, 1 H); 1.46 (*d*, $J = 6.6$, 3 H); 1.60 (*m*, 1 H); 1.93 (*ddd*, $J = 15.0$, 12.2, 3.0, 1 H); 3.02 (*s*, 3 H); 3.04 (*s*, 3 H); 3.06 (*s*, 3 H); 3.45 (*q*, $J = 6.7$, 1 H); 3.57 (*d*, $J = 15.3$, 1 H); 3.71 (*d*, $J = 18.7$, 1 H); 3.87 (*d*, $J = 18.5$, 1 H); 4.08 (*dd*, $J = 12.2$, 2.5, 1 H); 4.95 (*dd*, $J = 15.3$, 9.9, 1 H); 6.42 (*d*, $J = 9.7$, 1 H). Signals of the minor conformer were visible at 0.96 (*d*, $J = 13.8$) 3.08 (*s*), and 4.60 (*q*, $J = 7.2$). Integration of the 2 *q* at 3.45 and 4.60 indicated a conformer ratio of 3:1. ^{1}H-NMR in D_2O (200 MHz) showed only one Me *d*. ^{13}C-NMR (100 MHz, $CDCl_3$): 1.35 (*q*); 20.6 (*q*); 23.2 (*q*); 25.4 (*d*); 30.9 (*q*); 36.0 (*t*); 37.2 (*q*); 37.4 (*q*); 43.7 (*t*); 54.6 (*t*); 56.5 (*d*); 60.1 (*d*); 167.1 (*s*); 169.8 (*s*); 171.4 (*s*); 172.0 (*s*). FAB-MS: 363.2 (9, $[M + 23]^+$), 341.2 (62, $[M + 1]^+$), 137.0 (75).

*Cyclo(-Leu-Me-*L*-Ser-Sar-Gly-)* (**28c**). As described in the *General Procedure*, with **1** (0.050 g, 0.160 mmol), LiBr/THF (0.46 ml, 0.317 mmol), THF (3.42 ml), DMPU (0.12 ml, 0.960 mmol), and LDA (4.0 ml, 1.60 mmol). Simultaneously, a soln. of CH_2O in THF was prepared by heating α-polyoxymethylene [41] to 140° under a stream of Ar. The CH_2O gas was condensed in a flask cooled to −78° and then gradually warmed to r.t., while passing the resulting CH_2O gas with an Ar stream into a THF soln. at −78°. This CH_2O/THF soln. was kept at −78° under Ar and used immediately. After stirring the reaction soln. for 2 h at −78°, 5.0 ml of the CH_2O soln. was added *via* syringe, and the resulting cloudy/yellow soln. stirred overnight. The reaction soln. was then warmed to −55° for 2 h and quenched with AcOH (0.11 ml, 1.92 mmol, in 0.1 ml THF). After concentrating and treating with *Dowex*, the crude product was purified by prep. HPLC (*RP-C*$_4$, H_2O) giving three fractions: **28c** (t_R 13.5 min, co-eluted with DMPU), recovered **1** (t_R 26 min, co-eluted with a small amount of **28c**), 0.0052 g (10%), and **29c** (t_R 38.5 min), 0.0044 g (8%, this sample was not characterized). The DMPU was removed from **28c** by washing with toluene: 0.019 g (34%) for a combined yield of (42%). An anal. sample of **28c** was prepared by recrystallization from AcOEt/hexane, affording a colorless solid. M.p. 179–181° (dec., sealed tube). $[\alpha]_D = -193.2$ ($c = 0.30$, $CHCl_3$). IR (KBr): 3700–3000*s* (br.), 2955*m*, 1665*s*, 1529*w*, 1469*s*, 1399*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*d*, $J = 7.2$, 3 H); 1.01 (*d*, $J = 6.7$, 3 H); 1.24 (*ddd*, $J = 14.2$, 9.8, 2.1, 1 H); 1.55 (*m*, 1 H); 1.91 (*m*, 1 H); 3.07 (*s*, 3 H); 3.08 (*s*, 3 H); 3.18 (br. *s*, 1 H); 3.32 (*d*, $J = 15.0$, 1 H); 3.50 (*dd*, $J = 8.3$, 4.2, 1 H); 3.59 (*m*, 1 H); 3.75 (*d*, $J = 18.3$, 1 H); 3.90 (*d*, $J = 18.3$, 1 H); 3.91 (*m*, 1 H); overlapping *d* at 3.90; 4.32 (*m*, 1 H); 4.80 (*dd* $J = 15.2$, 9.7, 1 H); 7.79 (*d*, $J = 9.7$, 1 H); 8.50 (br. *d*, $J = 8.1$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.1 (*q*); 23.2 (*q*); 24.7 (*d*); 36.9 (*q*); 37.2 (*q*); 40.2 (*t*); 42.9 (*t*); 52.2 (*d*); 54.6 (*t*); 59.6 (*t*); 64.2 (*d*); 166.8 (*s*); 170.9 (*s*); 171.5 (*s*); 174.2 (*s*). FAB-MS: 365.0 (14, $[M + 23]^+$), 343.1 (20, $[M + 1]^+$), 307.0 (31), 176.0 (22), 137.0 (84), 107.0 (32).

*Cyclo(-Leu-Me-*L*-Ape(4-en)-Sar-Gly-)* (**28d**). As for **28b**, with **1** (0.050 g, 0.160 mmol), LiBr/THF (0.46 ml, 0.317 mmol), THF (5 ml), DMPU (0.12 ml, 0.960 mmol), LDA (4.0 ml, 1.60 mmol), CH_2=$CHCH_2Br$ (0.16 ml, 1.92 mmol), and AcOH (0.11 ml, 1.92 mmol, in 0.1 ml THF). Purification by prep. HPLC (*RP-C*$_8$, 8% → 15% MeCN/H_2O) gave 0.0249 g (50%) of recovered **1** and 0.014 g (25%) of **28c** as a colorless solid. An anal. sample was prepared by recrystallization from i-PrOH to give colorless, fine needles. M.p. 262.5–263.5° (dec., sealed tube). $[\alpha]_D = -288.9$ ($c = 0.45$, $CHCl_3$). IR (KBr): 3416*m* (br.), 3271*m*, 3071*w*, 2953*m*, 1691*s*, 1661*s*, 1608*s*, 1558*w*, 1528*s*,

1401*m*, 649*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, *J* = 6.6, 3 H); 1.02 (*d*, *J* = 6.7, 3 H); 1.22 (*ddd*, *J* = 14.2, 10.0, 2.2, 1 H); 1.56 (*m*, 1 H); 1.94 (*m*, 1 H); 2.90–2.70 (*m*, 2 H); 3.04 (*s*, 3 H); 3.05 (*s*, 3 H); 3.33 (*d*, *J* = 15.0, 1 H); 3.43 (*dd*, *J* = 8.6, 5.4, 1 H); 3.71 (*d*, *J* = 18.4, 1 H); 3.87 (*d*, *J* = 18.4, 1 H); 3.89 (*m*, 1 H); overlapping *d* at 3.87; 4.79 (*dd*, *J* = 15.2, 9.7, 1 H); 5.09 (*d*, *J* = 11.5, 1 H); 5.10 (*d*, *J* = 14.3, 1 H); 5.89 (*m*, 1 H); 7.76 (*d*, *J* = 9.5, 1 H); 8.66 (br. *d*, *J* = 7.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.1 (*q*); 23.3 (*q*); 24.6 (*d*); 33.9 (*t*); 37.5 (*q*); 38.2 (*q*); 40.2 (*t*); 43.0 (*t*); 52.2 (*d*); 54.7 (*t*); 64.5 (*d*); 118.3 (*t*); 135.3 (*d*); 167.4 (*s*); 169.8 (*s*); 171.4 (*s*); 173.8 (*s*). FAB-MS: 705.2 (31, $[2M + 1]^+$), 375.1 (17, $[M + 23]^+$), 353.1 (100, $[M + 1]^+$), 307.0 (16), 137.0 (48), 86.0 (46), 84.0 (80).

*Cyclo(-Val-*L*-(D$_1$)Sar-Sar-Gly-)* (**31a**). Solubilized at −78°, as described in the *General Procedure*; as described for **28a**, with **2** (0.050 g, 0.168 mmol), LiBr/THF (3.05 ml, 2.09 mmol), THF (2.87 ml), LDA (2.09 ml, 0.838 mmol), BuLi (0.34 ml, 0.503 mmol), and CF_3CO_2D (0.18 ml, 2.35 mmol). The product was purified by prep. HPLC (*RP-C$_8$*, 100% H_2O → 10% MeCN/H_2O): 0.0361 g (72%) of **2**/**31a**. ^{1}H-NMR (400 MHz, (D_6)DMSO) indicated a decrease in the integral of the *d* at 3.93 ppm, and the *d* at 4.21 beginning to collapse to a *s*, amounting to a D incorporation of 7.5%. ^{13}C-NMR (100 MHz, (D_6)DMSO) showed almost no noticeable change. FAB-MS: 322.2 (6, $[M + 23]^+$), 321.2 (14), 300.2 (44, $[M + 1]^+$), 299.2 (98), 289.0 (13), 200.1 (11), 136.0 (71), 120.0 (13), 107.0 (26), 90.0 (23).

Cyclo(-Val-MeAla-Sar-Gly-) (**31b**). As described in the *General Procedure*, with **2** (0.025 g, 0.0838 mmol), LiBr/THF (1.70 ml, 1.17 mmol), THF (2.5 ml), LDA (0.84 ml, 0.335 mmol), MeI (0.06 ml, 1.00 mmol), and AcOH (0.08 ml, 2.20 mmol). Purification by prep. HPLC (*RP-C$_8$*, 100% H_2O 5 min. → 5% MeCN/H_2O 40 min) gave 0.012 g (48%) of recovered **2**, and 0.0052 g (20%) of **31b** as a colorless solid. M.p. 170–175° (subl., sealed tube). The absolute configuration of the newly formed amino acid was determined by hydrolysis, derivatization, and GC [14]. $[\alpha]_D = -201.1$ (*c* = 0.25, $CHCl_3$). IR (KBr): 3419*m* (br.), 3293*m* (br.), 2962*m*, 2933*w*, 1660*s*, 1530*m*, 1456*m*, 1397*m*, 1090*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*d*, *J* = 7.0, 3 H); 1.06 (*d*, *J* = 6.8, 3 H); 1.43 (*d*, *J* = 6.6, 3 H); 2.08 (*m*, 1 H); 3.04 (*s*, 3 H); 3.08 (*s*, 3 H); 3.33 (*d*, *J* = 15.1, 1 H); 3.44 (*q*, *J* = 6.6, 1 H); 3.70 (*d*, *J* = 18.2, 1 H); 3.79 (*dd*, *J* = 9.7, 3.9, 1 H); 3.84 (*d*, *J* = 18.3, 1 H); 4.81 (*dd*, *J* = 15.0, 9.8, 1 H); 7.98 (*d*, *J* = 9.8, 1 H); 8.16 (*d*, *J* = 9.0, 1 H). ^{1}H-NMR (200 MHz, CD_3OD) indicated the presence of 3 conformers (3α-CH_3 signals) in a ratio of *ca.* 1.8:1.4:1. ^{13}C-NMR (100 MHz, $CDCl_3$): 13.4 (*q*); 15.8 (*q*); 20.0 (*q*); 28.9 (*d*); 36.6 (*q*); 37.7 (*q*); 43.2 (*t*); 54.9 (*t*); 58.7 (*d*); 60.0 (*d*); 167.3 (*s*); 170.7 (*s*); 171.6 (*s*); 172.0 (*s*). FAB-MS: 335.2 (30, $[M + 23]^+$), 313.2 (54, $[M + 1]^+$), 107.0 (25), 89.0 (21).

Cyclo(-Val-MeSer-Sar-Gly-) (**31c**). According to the *General Procedure*, and as described of **28c**, with **2** (0.050 g, 0.168 mmol), LiBr/THF (3.05 ml, 2.09 mmol), THF (2.87 ml), LDA (2.09 ml, 0.838 mmol), CH_2O/THF (4.0 ml), and AcOH (0.57 ml, 1.0 mmol. 1.75M in THF). The concentrated reaction mixture was purified by prep. HPLC (*RP-C$_8$*, H_2O) to give 0.020 g (36%) **31c** as a colorless solid, and 0.015 g (30%) of recovered **2**. M.p. 174–176° (dec.). $[\alpha]_D = -81.4$ (*c* = 0.30, MeOH). IR (KBr): 3416*m* (br.), 3284*m* (br.), 2963*w*, 1660*s*, 1533*m*, 1467*m*, 1399*m*, 1205*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*d*, *J* = 7.0, 3 H); 1.06 (*d*, *J* = 6.8, 3 H); 2.09 (*m*, 1 H); 3.09 (*s*, 3 H); 3.10 (*s*, 3 H); 3.32 (*d*, *J* = 15.0, 1 H); 3.48 (*dd*, *J* = 8.4, 4.1, 1 H); 3.58 (br. *d*, *J* = 10.2, 1 H); 3.74 (*d*, *J* = 18.3, 1 H); 3.81 (*dd*, *J* = 9.6, 3.8, 1 H); 3.88 (*d*, *J* = 18.4, 1 H); 4.32 (*dd*, *J* = 10.7, 8.4, 1 H); 4.81 (*dd*, *J* = 15.0, 9.8, 1 H); 7.96 (*d*, *J* = 9.7, 1 H); 8.02 (*d*, *J* = 9.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.8 (*q*); 19.9 (*q*); 28.9 (*d*); 37.2 (*q*); 37.3 (*q*); 43.2 (*t*); 54.6 (*t*); 58.6 (*d*); 59.8 (*t*); 64.5 (*d*); 166.7 (*s*); 171.0 (*s*); 172.0 (*s*); 172.5 (*s*). FAB-MS: 351.1 (14, $[M + 23]^+$), 329.1 (28, $[M + 1]^+$), 107.0 (22), 89.0 (19).

*Cyclo(-*D*-Ala-*D*-(D$_1$)Sar-MeLeu-Gly-)* (**32a**). As described in the *General Procedure*, with **3** (0.100 g, 0.310 mmol), LiBr/THF (5.59 ml, 4.14 mmol, 0.74M in THF), THF (5.0 ml), DMPU (0.15 ml, 1.23 mmol), LDA (2.09 ml, 0.838 mmol), BuLi (0.59 ml, 0.93 mmol), and CF_3CO_2D (0.33 ml, 4.29 mmol, in 1 ml THF). The reaction soln. was allowed to warm to r.t. overnight, concentrated, treated with basic and acidic *Dowex*, and purified by prep. HPLC (*RP-C$_8$*, 10% MeCN/H_2O): 0.091 g (91%). An anal. sample was prepared by recrystallization from CH_2Cl_2/hexane. $[\alpha]_D = -13.5$ (*c* = 0.98, H_2O). ^{1}H-NMR (400 MHz, $CDCl_3$) showed a decrease in the signal at 3.62 ppm (*d*, *J* = 17.8, H_o–C(11)) and the signal at 4.29 ppm (H_i–C(11)) collapsing to a *s*. Integration indicated a 65% D incorporation. ^{13}C-NMR (100 MHz, $CDCl_3$) showed a decrease in the intensity of the *t* at 50.9 ppm and the appearance of a D-coupled signal. ^{2}H-NMR (46 MHz, DMSO): 3.60 (br. *s*). FAB-MS: 350.2 (12, $[M + 23]^+$), 349.2 (5), 328.2 (100, $[M + 1]^+$), 327.2 (49), 155.1 (21), 136.0 (50), 100.1 (35).

*Cyclo(-*D*-Ala-Me-*D*-Ala-MeLeu-Gly-)* (**32b**). As described in the *General Procedure*, with **3** (0.050 g, 0.153 mmol), LiBr/THF (2.78 ml, 1.32 mmol), THF (3.19 ml), DMPU (0.11 ml, 0.919 mmol), LDA (1.92 ml, 0.766 mmol), MeI (0.11 ml, 1.84 mmol), and AcOH (0.52 ml, 0.919 mmol, 1.75M in THF). Purification by prep. HPLC (*RP-C$_4$*, H_2O 15 min. → 20% MeCN/H_2O 60 min) afforded 0.0092 g (18%) of recovered **3** and 0.024 g (46%) of **32b** as a colorless solid. The absolute configuration of the newly formed amino acid was determined by hydrolysis, derivatization, and GC [14] to be (*R*). An anal. sample was prepared by recrystallization from AcOEt. M.p. 237–239° (dec.). $[\alpha]_D = -12.2$ (*c* = 0.70, MeOH). IR (KBr): 3370*m*, 3070*w*, 2930*s*, 1700*s*, 1570*w*, 1450*m*, 1375*m*,

1265*w*, 1085*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, *J* = 6.5, CH_3–C(14)); 0.95 (*d*, *J* = 6.4, CH_3–C(14)); 1.30 (*d*, *J* = 6.5, CH_3–C(18)); 1.44 (*m*, *J* = 7.2, 2 H–C(13)); 1.54 (*d*, *J* = 7.2, CH_3–C(11)), overlapping with *m* at 1.44; 1.76 (*m*, 1 H, H–C(14)); 2.79 (*s*, CH_3–N(1)); 3.12 (*s*, CH_3–N(10)); 3.59 (*dd*, *J* = 17.4, 6.7, H_o–C(5)); 3.59 (*dd*, *J* = 17.3, 9.4, H_i–C(5)); 4.50 (*q*, *J* = 7.2, H_i–C(11)); 4.91 (*m*, H_i–C(8)); 5.32 (*dd*, *J* = 8.2, 6.2, H_i–C(2)); 5.88 (*d*, *J* = 8.8, H–N(7)); 5.25 (*dd*, *J* = 9.5, 6.7, H–N(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.2 (*q*); 17.5 (*q*); 22.6 (*q*); 23.1 (*q*); 24.4 (*d*); 31.0 (*q*); 31.1 (*q*); 37.0 (*t*); 43.7 (*t*); 45.8 (*d*); 51.9 (*d*); 52.4 (*d*); 167.1 (*s*); 171.2 (*s*); 172.1 (*s*); 172.4 (*s*). FAB-MS: 363.2 (45, $[M + 23]^+$), 341.2 (94, $[M + 1]^+$), 256.2 (14), 176.1 (13), 100.1 (33).

Cyclo(-D-*Ala-Me*-D-*Ser-MeLeu-Gly-)* (**32c**). As for **28c**, with **3** (0.050 g, 0.153 mmol), LiBr/THF (2.78 ml, 1.32 mmol), THF (3.19 ml), DMPU (0.11 ml, 0.919 mmol), LDA (1.92 ml, 0.766 mmol), CH_2O/THF (5.0 ml), and AcOH (0.52 ml, 0.919 mmol, 1.75M in THF). Purification twice by prep. HPLC (*RP-C*$_4$, 0.1% TFA/H_2O 6 min → 20% MeCN 50 min), followed by recrystallization from CH_2Cl_2 gave 0.019 g (34%) of **32c**. Due to the polar nature of this compound, purification was quite difficult. An anal. sample was prepared by an additional HPLC purification (*RP-C*$_4$, H_2O). Colorless solid. M.p. 210–212° (dec., sealed tube). $[\alpha]_D = -22.5$ (*c* = 0.42, MeOH). IR (KBr): 3289*m* (br.), 3087*w*, 2980*m*, 1774*w*, 1680*s*, 1655*s*, 1569*m*, 1475*m*, 1455*m*, 1076*s*, 1007*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.86 (app. *t*, *J* = 6.2, 6 H); 1.05 (*d*, *J* = 6.5, 3 H); 1.25 (*m*, 1 H); 1.38 (*m*, 1 H); 1.59 (*m*, 1 H); 2.66 (*s*, 3 H); 2.01 (*s*, 3 H); 3.31 (*dd*, *J* = 17.6, 6.9, 1 H), overlapping H_2O signal at 3.33; 3.64 (*dd*, *J* = 17.5, 8.6, 1 H); 3.73 (*m*, 2 H); 4.52 (*dd*, *J* = 7.8, 4.7, 1 H); 4.80 (*m*, 1 H); 5.05 (*m*, 2 H); 7.77 (app. *t*, *J* = 7.4, 1 H); 8.13 (*d*, *J* = 9.2, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 17.5 (*q*); 22.6 (*q*); 22.7 (*q*); 23.7 (*d*); 30.2 (*q*); 30.3 (*q*); 36.9 (*t*); 42.8 (*t*); 43.9 (*d*); 51.2 (*d*); 57.6 (*t*); 59.6 (*d*); 167.0 (*s*); 168.6 (*s*); 171.39 (*s*); 171.43 (*s*). FAB-MS: 379.1 (24, $[M + 23]^+$), 357.1 (89, $[M + 1]^+$), 351 (24), 256.2 (14), 176.1 (13), 136.1 (82), 100.1 (77), 73.9 (91).

Cyclo(-D-*Ala-Me*-D-*Ape(4-en)-MeLeu-Gly-)* (**32d**). According to the *General Procedure*, with **3** (0.050 g, 0.153 mmol), LiBr/THF (2.78 ml, 1.32 mmol), THF (3.19 ml), DMPU (0.11 ml, 0.919 mmol), LDA (1.92 ml, 0.766 mmol), CH_2=$CHCH_2Br$ (0.16 ml, 1.84 mmol), and AcOH (0.52 ml, 0.919 mmol, 1.75M in THF). HPLC purification (*RP-C*$_4$, H_2O 15 min → 20% MeCN 60 min) gave 0.0083 g (17%) recovered **3** and 0.039 g (70%) of **32d** as a colorless solid. M.p. 224–226° (dec.) $[\alpha]_D = -24.4$ (*c* = 0.50, MeOH); $[\alpha]_D = -39.0$ (*c* = 0.50, $CHCl_3$). IR (KBr): 3286*m*, 3076*s*, 2953*m*, 1656*s*, 1550*w*, 1448*m*, 1386*m*, 1074*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.939 (*d*, *J* = 6.5, 3 H); 0.944 (*d*, *J* = 6.4, 3 H); 1.30 (*d*, *J* = 6.5, 3 H); 1.44 (*m*, 2 H); 1.78 (*m*, 1 H); 2.47 (*m*, 1 H); 2.69 (*m*, 1 H); 2.80 (*s*, 3 H); 3.13 (*s*, 3 H); 3.60 (*dd*, *J* = 17.4, 6.7, 1 H); 3.87 (*dd*, *J* = 17.3, 9.4, 1 H); 4.40 (*dd*, *J* = 11.6, 2.8, 1 H); 4.93 (*m*, 1 H); 5.18 (*m*, 1 H); 5.21 (*dd*, *J* = 11.0, 1.2, 1 H); 5.31 (*m*, 1 H); 5.69 (*m*, 1 H); 6.18 (*d*, *J* = 9.1, 1 H); 6.48 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.5 (*q*); 22.6 (*q*); 23.1 (*q*); 24.4 (*d*); 31.1 (*q*); 31.3 (*q*); 32.0 (*t*); 37.1 (*t*); 43.7 (*t*); 45.6 (*d*); 52.1 (*d*); 57.3 (*d*); 118.9 (*t*); 132.5 (*d*); 167.2 (*s*); 170.9 (*s*); 171.9 (*s*); 172.5 (*s*). FAB-MS: 733.4 (7, $[2M + 23]^+$), 389.2 (12, $[M + 23]^+$), 367.2 (100, $[M + 1]^+$), 256.1 (7), 84 (58).

Cyclo(-D-*Ala-Me*-D-*Phe-MeLeu-Gly-)* (**32e**). According to the *General Procedure*, with **3** (0.050 g, 0.153 mmol), LiBr/THF (2.78 ml, 1.32 mmol), THF (3.19 ml), DMPU (0.11 ml, 0.919 mmol), LDA (1.92 ml, 0.766 mmol), $PhCH_2Br$ bromide (0.22 ml, 1.84 mmol), and AcOH (0.52 ml, 0.919 mmol, 1.75M in THF). The reaction mixture was concentrated and dried as usual, and the resulting colorless foam taken up in H_2O and washed with CH_2Cl_2. The aq. phase was purified by HPLC (*RP-C*$_4$, H_2O 15 min → 20% MeCN 50 min) to give 0.0094 g (19%) of recovered **3**. The combined org. phases were dried, concentrated, and purified by radial chromatography (1-mm plate, 5% MeOH/CH_2Cl_2). The resulting product was further separated from DMPU by recrystallizing three times

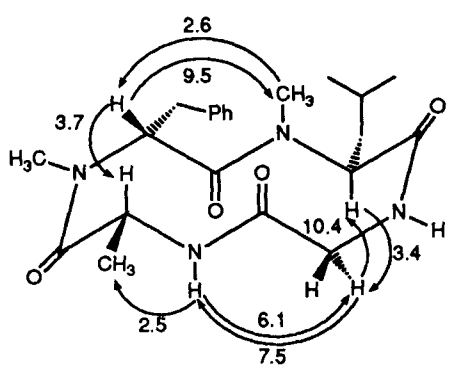

Fig. 13. *DNOE* (300 MHz, $CDCl_3$) *Results for* **32e**

from $CHCl_3$/hexane, yielding 0.0224 g (34%) of **32e** as a colorless solid. M.p. 140–142°. $[\alpha]_D = -52.1$ ($c = 1.03$, MeOH). IR (KBr): 3420*w* (br.), 3270*m*, 3060*w*, 2950*m*, 1735*s*, 1700*s*, 1555*w*, 1455*m*, 1075*m*, 700*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.97 (*d*, $J = 6.3$, CH_3–C(14)); 0.98 (*d*, $J = 6.2$, CH_3–C(14)); 1.26 (*d*, $J = 6.5$, CH_3–C(8)); 1.50 (*m*, 2 H–C(13)); 1.81 (*m*, H–C(14)); 2.90 (*s*, CH_3–N(1)); 3.13 (*s*, CH_3–N(10)); 3.14 (*m*, 2 HCH_2–C(11)), overlapping *s* at 3.13; 3.62 (*dd*, $J = 17.4, 6.7$, H_o–C(5)); 3.88 (*dd*, $J = 17.3, 9.4$, H_i–C(5)); 4.76 (*dd*, $J = 11.1, 3.4$, H_i–C(11)); 4.88 (*m*, H_i–C(8)); 5.46 (app. *t*, $J = 7.8$, H_i–C(2)); 5.96 (*d*, $J = 9.1$, H–N(7)); 6.31 (*dd*, $J = 9.0, 6.9$, H–N(4)); 7.18 (*d*, $J = 1.4$, 2 H); 7.31 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.5 (*q*); 22.7 (*q*); 23.1 (*q*); 24.5 (*d*); 31.4 (*q*); 31.7 (*q*); 37.6 (*t*); 43.7 (*t*); 45.7 (*d*); 52.2 (*d*); 58.1 (*d*); 127.6 (*d*); 127.7 (*d*); 129.2 (*d*); 135.9 (*s*); 167.1 (*s*); 171.0 (*s*); 171.8 (*s*); 172.4 (*s*). FAB-MS: 439.2 (8, $[M + Na]^+$), 417.2 (52, $[M + 1]^+$), 307.1 (37), 289.1 (18), 176.0 (12), 107.0 (28). Anal. calc. for $C_{22}H_{32}N_4O_4$: C 63.44, H 7.74, N 13.45; found: C 63.65, H 7.81, N 13.58.

6. *Alkylation of* **1** *and* **3** *Under 'Thermodynamic' Conditions.* As described in the *General Procedure*, with **1** (0.025 g, 0.0080 mmol), LiBr/THF (0.81 ml, 0.560 mmol), THF (3.13 ml), DMPU (0.058 ml, 0.480 mmol), LDA (1.0 ml, 0.400 mmol). The resulting clear colorless soln. was warmed to r.t. for 1.5 h. while stirring. After re-cooling the resulting cloudy soln. to –78°, MeI (0.060 ml, 0.960 mmol) was added, the soln. stirred at –78° for 18 h, and the reaction quenched with AcOH (0.025 ml, 0.44 mmol, in 0.1 ml THF). Workup and purification as described for **28b** afforded 0.0121 g (48%) of recovered **1** and 0.0031 g (12%) of **29b**. Anal. HPLC (*RP-C_8*) indicated a 3.2:1 ratio of **29b**/**28b**; however, the latter product was not isolated due to poor resolution on the prep. *RP-C_4* HPLC column.

*Cyclo(*D*-Ala-Me-*L*-Ala-MeLeu-Gly-)* (**33**). The above procedure was repeated with **3** (0.100 g, 0.306 mmol), LiBr/THF (5.74 ml, 4.23 mmol, 0.72M in THF), THF (5.0 ml), DMPU (0.15 ml, 1.23 mmol), and LDA (3.0 ml, 1.04 mmol). The resulting turbid soln. was stirred at –78° for 1.5 h. and at r.t. for 1 h., whereupon the soln. cleared. After re-cooling the soln. to –78° MeI (0.11 ml, 1.84 mmol) was added, and the soln. stirred overnight. Upon quenching with AcOH (0.07 ml, 1.22 mmol), workup, and purification by HPLC (*RP-C_4*, $H_2O \rightarrow 5\%$ MeCN), 0.054 g (54%) of **1**, 0.0068 g (6.5%) of **33**, and 0.0065 g (6.2%) of **32b** were isolated. The absolute configuration of the newly formed amino acid in **33** was determined by hydrolysis, derivatization, and GC [14] to be (*S*). M.p.

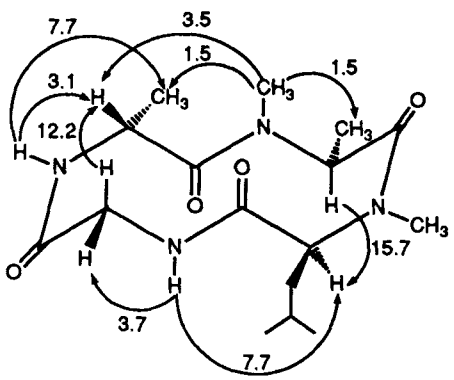

Fig. 14. *DNOE* (300 MHz, $CDCl_3$) *Results for* **33**

157–158°. $[\alpha]_D = -23.3$ ($c = 0.30$, MeOH). IR (thin film): 3270*m*, 3097*s*, 2957*m*, 1660*s*, 1557*m*, 1462*m*, 1407*m*, 734*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.93 (*d*, $J = 6.0$, CH_3–C(14)); 0.96 (*d*, $J = 6.2$, CH_3–C(14)); 1.27 (*d*, $J = 6.6$, CH_3–C(2)); 1.41 (*d*, $J = 7.0$, CH_3–C(11)); 1.45–1.60 (*m*, 2 H–C(13)); 1.97 (app. *t*, $J = 11.8$, H–C(14)); 2.76 (*s*, CH_3–N(4)); 3.05 (*s*, CH_3–N(1)); 3.27 (*d*, $J = 14.2$, H_o–C(8)); 4.19 (*m*, H_i–C(5), H_i–C(11)); 4.70 (*dd*, $J = 14.2$, 9.5, H_i–C(8)); 5.49 (*q*, $J = 6.7$, H_i–C(2)); 7.70 (*d*, $J = 9.5$, H–C(7)); 8.95 (*d*, $J = 8.1$, H–C(10)). *Decoupling experiments* (300 MHz, $CDCl_3$): Irradiating the *d* at 8.95 caused a change in the *m* at 4.19. Irradiating the *d* at 7.70 caused the *dd* at 4.70 to collapse to a *d* ($J = 14$). Irradiating the *q* at 5.49 caused the *d* at 1.27 to collapse to a *s*. Irradiating the *dd* at 4.70 caused the *d* at 7.70 and at 3.27 to collapse to *s*. Irradiating the *m* at 4.19 caused the *d* at 8.95 to collapse to a *s*, the app. *t* at 1.97 to collapse to a *m*, and a change in the *m* at 1.45–1.60. ^{13}C-NMR (100 MHz, $CDCl_3$): 14.2 (*q*); 18.0 (*q*); 20.7 (*q*); 23.3 (*q*); 25.0 (*d*); 29.9 (*q*); 30.4 (*q*); 39.1 (*t*); 42.8 (*t*); 48.9 (*d*); 50.0 (*d*); 57.2 (*d*); 170.5 (*s*); 171.2 (*s*); 172.0 (*s*); 172.7 (*s*). FAB-MS: 363.2 (34, $[M + Na]^+$), 341.3 (100, $[M + 1]^+$), 307.1 (10), 256.2 (10), 176.1 (14), 100.1 (25).

7. *Alkylation of* **3** *'Solubilized' at Room Temperature. Cyclo(-*D*-Me-Ala-Sar-MeLeu-Gly-)* (**34**) *and Cyclo(-*D*-Me-Ala-Sar-MeLeu-Sar-)* (**35**). To **3** (0.100 g, 0.306 mmol) and LiBr (0.226 g, 2.61 mmol) was added DMPU (0.15 ml, 1.23 mmol) and THF (8 ml). The heterogeneous soln. was cooled to −78°, LDA (1.04 mmol in 3 ml THF) was added and, after 5 min, the soln. was stirred at r.t. for 1 h. Upon addition of more LiBr (0.142 g, 1.64 mmol) at r.t., solubilization occurred. After cooling the resulting clear, pale-yellow soln. to −78°, MeI (0.23 ml, 3.68 mmol) was added and the soln. was allowed to warm to r.t. overnight while stirring. Addition of AcOH (0.06 ml, 1.05 mmol), followed by concentrating and purification by HPLC (*RP-C_8*, 10% $CH_3CN/H_2O \rightarrow 15\%$), gave 0.0548 g (55%) of recovered **3**, 0.028 g (27%) of **34**, and 0.0031 g (3%) of **35**.

Data of **34**: colorless solid. M.p. 208–210°. $[\alpha]_D = +18.4$ ($c = 0.36$, MeOH). IR (thin film): 3283*m*, 2956*m*, 1654*s*, 1560*w*, 1458*m*, 1400*m*, 1291*w*, 1084*w*, 948*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.6$, 3 H); 0.97 (*d*, $J = 6.6$, 3 H); 1.27 (*d*, $J = 6.7$, 3 H); 1.57 (*m*, 2 H); 1.71 (*m*, 1 H); 2.72 (*s*, 3 H); 2.74 (*s*, 3 H); 3.08 (*s*, 3 H); 3.57 (*dd*, $J = 17.12, 5.8$, 1 H); 3.60 (*d*, $J = 17.8$, 1 H); 4.25 (*dd*, $J = 17.6, 10.1$, 1 H); 4.41 (*d*, $J = 17.7$, 1 H); 5.29 (*dd*, $J = 8.3, 6.1$, 1 H); 5.44 (*q*, $J = 6.9$, 1 H); 5.94 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1 (*q*); 22.6 (*q*); 23.0 (*q*); 24.5 (*d*); 28.5 (*q*); 29.0 (*q*); 36.5 (*t*); 36.7 (*q*); 43.0 (*t*); 49.0 (*d*); 50.8 (*t*); 50.9 (*d*); 167.6 (*s*); 167.7 (*s*); 170.4 (*s*); 172.1 (*s*). FAB-MS: 363.2 (22, $[M + 23]^+$), 341.2 (100, $[M + 1]^+$), 154.0 (23), 136.0 (20), 100.0 (32), 57.9 (46).

Data of **35**: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.6$, 3 H); 0.96 (*d*, $J = 6.5$, 3 H); 1.53 (*m*, 2 H); 1.74 (*m*, 1 H); 2.68 (*d*, 3 H); 2.71 (*d*, 3 H); 3.08 (*s*, 6 H); 3.57 (*d*, $J = 17.8$, 1 H); 3.58 (*d*, $J = 17.7$, 1 H); 4.41 (*d*, $J = 17.7$, 1 H); 4.46 (*d*, $J = 17.7$, 1 H); 5.31 (*dd*, $J = 8.2, 6.1$, 1 H); 5.43 (*q*, $J = 6.7$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1 (*q*); 22.7 (*q*); 23.1 (*q*); 24.5 (*d*); 28.6 (*q*); 28.9 (*q*); 36.7 (*q*); 36.7 (*q*); 37.4 (*t*); 48.9 (*d*); 50.6 (*t*); 50.6 (*t*); 51.7 (*d*); 167.1 (*s*); 167.3 (*s*); 170.1 (*s*); 170.4 (*s*). FAB-MS: 377.2 (8, $[M + 23]^+$), 355.2 (89, $[M + 1]^+$), 307.1 (36), 289.1 (19), 176.0 (20), 154.1 (100), 137.0 (79), 107.0 (28), 89.0 (26), 76.9 (23).

8. *Synthesis of* **28b** *and* **29b** via *Cyclization. Boc-Leu-MeAla-OCH_2Ph* (**36**). As described for **4**, with Boc-leucine (9.87 g, 39.6 mmol), Et(i-Pr)$_2$N (13.6 ml, 79.2 mmol), BOP-Cl (11.08 g, 43.5 mmol), CH_2Cl_2 (200 ml), alanine benzyl ester hydrochloride (10.0 g, 43.5 mmol), Et(i-Pr)$_2$N (8.20 ml, 47.9 mmol), and CH_2Cl_2 (155 ml). Purification by FC (20% → 25% AcOEt/hexane) gave 13.87 g (86%) of **36** as a colorless oil. $[\alpha]_D = -64.4$ ($c = 1.05$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*d*, $J = 6.6$, 3 H); 0.95 (*d*, $J = 6.4$, 3 H); 1.30–1.45 (*m*, 2 H); 1.42 (*d*, $J = 7.3$, 3 H); 1.43 (*s*, 9 H); 1.71 (*m*, 1 H); 2.94 (*s*, 3 H); 4.62 (*dt*, $J = 9.2, 4.4$, 1 H); 5.13 (*ABq*, $\nu_B = 5.17$, $\nu_A = 5.09$, $J = 12.2$, 2 H); 5.19 (*m*, 1 H); 5.34 (*q*, $J = 7.3$, 1 H); 7.34 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.2 (*q*); 21.7 (*q*); 23.4 (*q*); 24.6 (*d*); 28.4 (*q*); 30.9 (*q*); 42.4 (*t*); 49.0 (*d*); 52.2 (*d*); 67.0 (*t*); 79.5 (*s*); 128.3 (*d*); 128.4 (*d*); 128.6 (*d*); 135.5 (*s*); 155.7 (*s*); 171.5 (*s*); 173.5 (*s*). FAB-MS: 429.3 (19, $[M + 23]^+$), 407.3 (69, $[M + 1]^+$), 351.2 (30), 307.2 (46), 243.2 (35), 194.1 (39), 130.1 (29), 91.0 (100).

Boc-Leu-MeAla-OH (**37**). As described for **5**, with **36** (13.48 g, 33.2 mmol), MeOH (100 ml), and 10% Pd/C (0.674 g): 10.44 g (99%) of **37** as a colorless foam. $[\alpha]_D = -54.7$ ($c = 1.00$, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, $J = 6.6$, 3 H); 1.00 (*d*, $J = 6.0$, 3 H); 1.43 (*s*, 9 H); 1.44 (*d*, $J = 7.3$, 3 H); 1.45 (*m*, 2 H); 1.47 (*m*, 1 H); 3.04 (*s*, 3 H); 4.66 (*dt*, $J = 7.4$, 1 H); 5.42 (*d*, $J = 9.0$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1 (*q*); 21.7 (*q*); 23.4 (*q*); 24.6 (*d*); 28.4 (*q*); 31.3 (*q*); 41.9 (*t*); 49.1 (*d*); 52.4 (*d*); 79.7 (*s*); 155.8 (*s*); 174.2 (*s*); 175.4 (*s*). FAB-MS: 655.3 (11, $[2M + 23]^+$), 633.3 (7, $[2M + 1]^+$), 339.1 (67, $[M + 23]^+$), 317.2 (84, $[M + 1]^+$), 261.1 (82), 243.1 (20), 217.1 (96), 104.0 (100), 86.0 (89).

*Boc-Leu-Me-*D*-Ala-Sar-OCH_2Ph* (**38**) *and Boc-Leu-Me-*L*-Ala-Sar-OCH_2Ph* (**39**). As described for **4**, with **37** (10.34 g, 32.7 mmol), Et(i-Pr)$_2$N (11.2 ml, 65.4 mmol), BOP-Cl (9.15 g, 35.9 mmol), CH_2Cl_2 (165 ml), sarcosine benzyl ester toluene-4-sulfonate (12.63 g, 35.9 mmol), Et(i-Pr)$_2$N (6.8 ml, 39.5 mmol), and CH_2Cl_2 (130 ml). Purification by FC (50% AcOEt/hexane) gave a mixture of **38** and **39**. Attempted separation by MPLC (*Büchi* apparatus, 50% AcOEt/hexane, silica gel) provided 3.044 g of partially enriched **38** (higher R_f, amino-acid analysis [14] indicated D-MeAla) and 8.490 g of a mixture of **38** and **39**, for a total yield of 11.53 g (74%). These two fractions were carried on separately without further purification.

*Boc-Leu-Me-*D*-Ala-Gly-OH* (**45**) *and Boc-Leu-Me-*L*-Ala-Sar-Gly-OH* (**40**). As for **5**, with enriched **38** (3.04 g, 6.36 mol), MeOH (100 ml), and 10% Pd/C (0.152 g): 2.47 g (99%) of enriched **45** as a colorless foam. Likewise, with the mixture **38**/**39** (8.49 g, 17.8 mmol), MeOH (100 ml), and 10% Pd/C (0.424 g): 6.85 g of **45**/**40** (99%).

*Boc-Leu-Me-*D*-Ala-Sar-Gly-OCH_2Ph* (**46**) *and Boc-Leu-Me-*L*-Ala-Sar-Gly-OCH_2Ph* (**41**). As described for **12**, with enriched **45** (2.47 g, 6.37 mmol), NMM (0.70 ml, 6.37 mmol), isobutyl chloroformate (0.83 ml, 6.37 mmol), THF (30 ml), glycine benzyl ester toluene-4-sulfonate (2.17 g, 6.44 mmol), NMM (0.71 ml, 6.44 mmol), and DMF (12 ml). Extractive workup gave 3.20 g (94%) of enriched **46**. Likewise, with **45**/**40** (6.85 g, 17.7 mmol), NMM (1.95 ml, 17.7 mmol), isobutyl chloroformate (2.31 ml, 17.7 mmol), THF (80 ml), glycine benzyl ester toluene-4-sulfonate (6.02 g, 17.8 mmol), NMM (1.97 ml, 17.8 mmol), and DMF (30 ml): 8.52 g (90%) of **46**/**41**. Separation of the

distereoisomers was accomplished in 0.75-g batches *via* radial chromatography (4-mm plate, 5% MeOH/CH_2Cl_2).

Data of **46**: higher R_f fraction. Colorless foam. $[\alpha]_D = +55.1$ ($c = 1.00$, EtOH). IR (thin film): 3314*m*, 3040*w*, 2958*m*, 1749*m*, 1698*s*, 1638*s*, 1522*m*, 1176*s*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 180°): 0.888 (*d*, $J = 6.6$, 3 H); 0.894 (*d*, $J = 6.6$, 3 H); 1.15 (*d*, $J = 6.7$, 3 H); 1.37 (*s*, 9 H); 1.30–1.55 (*m*, 2 H); 1.60–1.75 (*m*, 1 H); 2.85 (*s*, 3 H); 2.89 (*s*, 3 H); 3.80–4.15 (*m*, 2 H); 3.92 (*d*, $J = 5.9$, 1 H); 4.42 (*dt*, $J = 8.8$, 4.6, 1 H); 5.13 (*s*, 2 H); 5.28 (br. *q*, $J = 6.8$, 1 H); 6.18 (br. *s*, 1 H); 7.33 (*m*, 5 H); 7.86 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D$_6$)DMSO, 180°): 14.2; 21.6; 22.8; 24.3; 28.2; 29.6; 49.4; 51.5; 65.9; 78.4; 127.6; 127.8; 128.2; 136.0; 155.1; 168.4; 169.2; 170.7; 172.0. FAB-MS: 557.2 (33, $[M + 23]^+$), 535.2 (11, $[M + 1]^+$), 457.2 (10), 435.2 (8), 299.1 (52), 243.1 (84), 199.1 (17), 130.1 (20), 91.0 (40).

Data of **41**: lower R_f fraction. Colorless foam. $[\alpha]_D = -85.2$ ($c = 1.00$, EtOH). IR (thin film): 3305*m*, 3040*w*, 2958*m*, 1705*m*, 1700*s*, 1637*s*, 1523*m*, 1407*m*, 1176*s*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 180°): 0.88 (*d*, $J = 6.6$, 3 H); 0.90 (*d*, $J = 6.6$, 3 H); 1.76 (*d*, $J = 6.7$, 3 H); 1.37 (*s*, 9 H); 1.40–1.50 (*m*, 2 H); 1.70 (*m*, 1 H); 2.85 (*s*, 3 H); 2.89 (*s*, 3 H); 3.88 (*d*, $J = 16.3$, 1 H); 3.92 (*d*, $J = 5.8$, 2 H); 4.01 (*d*, $J = 16.3$, 1 H); 4.42 (*m*, 1 H); 5.13 (*s*, 2 H); 5.28 (br. *m*, 1 H); 6.21 (br. *d*, $J = 7.4$, 1 H); 7.33 (*m*, 5 H); 7.90 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D$_6$)DMSO, 180°): 14.1; 21.5; 22.8; 24.3; 28.2; 29.6; 34.9; 49.3; 49.6; 51.0; 65.9; 78.3; 127.6; 127.8; 128.2; 136.0; 155.1; 168.4; 169.2; 170.8; 172.1. FAB-MS: 557.2 (42, $[M + 23]^+$), 535.2 (14, $[M + 1]^+$), 457.2 (9), 299.1 (56), 243.1 (88), 199.1 (7), 130.1 (18), 91.0 (40).

*Boc-Leu-Me-*L*-Ala-Sar-Gly-OH* (**42**). As described for **5**, with **41** (1.27 g, 2.38 mmol), MeOH (75 ml), and 10% Pd/C (0.064 g): 1.16 g (99%) of **42** as a colorless foam. $[\alpha]_D = -130.5$ ($c = 1.04$, EtOH). IR (thin film): 3307*m* (br.), 2964*m*, 1692*s* (br.), 1634*s* (br.), 1538*m*, 1409*m*, 1170*m*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 180°): 0.89 (*d*, $J = 6.6$, 3 H); 0.90 (*d*, $J = 6.6$, 3 H); 1.17 (*d*, $J = 6.7$, 3 H); 1.38 (*s*, 9 H); 1.30–1.54 (*m*, 2 H); 1.66 (*m*, 1 H); 2.86 (*s*, 3 H); 2.89 (*s*, 3 H); 3.76 (*d*, $J = 5.4$, 1 H); 3.87 (*d*, $J = 16.3$, 1 H); 4.05 (*d*, $J = 16.3$, 1 H); 4.41 (*m*, 1 H); 5.28 (br. *q*, $J = 6.6$, 1 H); 6.20 (br. *d*, $J = 6.8$, 1 H); 7.68 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D$_6$)DMSO, 180°): 14.1; 21.5; 22.8; 24.3; 28.2; 29.6; 34.9; 49.2; 49.6; 51.1; 78.3; 155.1; 168.1; 170.3; 170.8; 172.1. FAB-MS: 467.2 (100, $[M + 23]^+$), 445.3 (10, $[M + 1]^+$), 367.2 (15), 299.2 (62), 243.1 (87), 130.1 (19).

*Boc-Leu-Me-*D*-Ala-Sar-Gly-OH* (**47**). As for **5**, with **46** (1.27 g, 2.38 mmol). MeOH, (75 ml), and 10% Pd/C (0.064 g): 1.11 g (99%) of **42** as a colorless foam, $[\alpha]_D = +56.6$ ($c = 1.00$, EtOH). IR (thin film): 3318*m* (br.), 2959*m*, 1692*s*, 1634*s*, 1552*m*, 1408*m*, 1169*m*, 736*w*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 180°): 0.889 (*d*, $J = 6.6$, 3 H); 0.895 (*d*, $J = 6.6$, 3 H); 1.16 (*d*, $J = 6.7$, 3 H); 1.37 (*s*, 9 H); 1.29–1.55 (*m*, 2 H); 1.71 (*m*, 1 H); 2.87 (*s*, 3 H); 2.90 (*s*, 3 H); 3.76 (*d*, $J = 5.4$, 1 H); 3.84–4.10 (*m*, 2 H); 4.42 (*dt*, $J = 8.8$, 4.7, 1 H); 5.29 (br. *q*, $J = 5.1$, 1 H); 6.20 (br. *s*, 1 H); 7.65 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, (D$_6$)DMSO, 180°): 14.2; 21.6; 22.8; 24.3; 28.2; 29.6; 35.0; 49.4; 51.2; 78.4; 155.0; 168.1; 170.4; 170.7; 172.0. FAB-MS: 467.3 (90, $[M + 23]^+$), 445.3 (6, $[M + 1]^+$), 367.2 (18), 299.2 (48), 243.1 (78). 199.2 (18), 130.1 (19).

*Boc-Leu-Me-*L*-Ala-Sar-Gly-OPFP* (**43**) *and Boc-Leu-Me-*L*-Ala-Sar-Gly-OPFP Trifluoroacetate* (**44**). As described for **10** and **11**, with **42** (0.500 g, 1.12 mmol), pyridine (10 ml), pentafluorophenol trifluoroacetate (0.378 g, 1.35 mmol), and 50% CF_3COOH in CH_2Cl_2 (30 ml): 0.244 g (35%) of the crude **44** as a brown, viscous oil, which was cyclized to **28b** immediately.

*Boc-Leu-Me-*D*-Ala-Sar-Gly-OPFP* (**48**) *and Boc-Leu-Me-*D*-Ala-Sar-Gly-OPFP Trifluoroacetate* (**49**). With **47** (2.60 g, 5.85 mmol), pyridine (20 ml), pentafluorophenol trifluoroacetate (4.1 g, 14.6 mmol), and 30% CF_3COOH in CH_2Cl_2 (90 ml): 4.19 g of the crude **44** as a brown oil, which was cyclized to **29b** immediately.

Cyclization of **44** *to 'Authentic' Cyclo(-Leu-Me-*L*-Ala-Sar-Gly-)* (**28b**). As described for **1**, with dioxane (260 ml), pyridine (78 ml), 2,2,2-trifluoroethanol (6 ml), DMAP (0.038 g, 0.312 mmol), **44** (*ca.* 0.25 g, 0.4 mmol), and dioxane (50 ml). Following treatment with *Dowex*, the crude reaction mixture was purified by radial chromatography (4-mm plate, 5% → 7% MeOH/CH_2Cl_2). Repeated recrystallization from AcOEt/hexane was not successful, so the product was purified by HPLC (*RP-C$_8$*, 8% MeCN/H_2O), to give 0.0159 g (12%) of **28b**. M.p. 163–165°. $[\alpha]_D = -221.4$ ($c = 0.35$, $CHCl_3$). Spectral data (IR, NMR, MS) are identical with those of **28b** obtained by alkylation of **1**.

Cyclization of **49** *to 'Authentic' Cyclo(-Leu-Me-*D*-Ala-Sar-Gly-)* (**29b**). As described for **1**, with dioxane (4 l), pyridine (1019 ml), 2,2,2-trifluoroethanol (76 ml), DMAP (0.571 g, 4.68 mmol), **49** (*ca.* 3.65 g, 5.84 mmol), and dioxane (748 ml). Purification by radial chromatography (4-mm plate, 3% MeOH/CH_2Cl_2), followed by HPLC (*RP-C$_8$*, 8% MeCN/H_2O), to give 0.214 g (14%) of **29b**. M.p. 199.5–201° (dec.). $[\alpha]_D = -40.1$ ($c = 0.90$, $CHCl_3$). Spectral data (IR, NMR, MS) are identical with those of **29b** obtained by alkylation of **1**.

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