101. Modification of Cyclosporin A (CS)[1]): Generation of an Enolate at the Sarcosine Residue and Reactions with Electrophiles

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Strong bases (lithium diisopropylamide (LDA) or BuLi) convert cyclosporin A (CS) to a hexalithio derivative containing a Li alkoxide, four Li azaenolate, and one Li enolate units. The Li_6 compound is solubilized in tetrahydrofuran (THF) by addition of excess LDA or LiCl. Reactions with electrophiles (alkyl halides, aldehydes, $ClCO_2R$, CO_2, $(RS)_2$, D_2O) at low temperatures give products containing new side chains in amino-acid residue 3 of the cyclic undecapeptide (see **1**–**13**, *Schemes 1* and *2*, and *Figs. 1* and *2*) in moderate to high yields and, with *Re*- or *Si*-selectivities, depending upon the conditions of lithiation of up to 7:1. Pure CS derivatives (*Scheme 2*, *Table 1* in the *Exper. Part*) can be isolated by column chromatography. *N*-Alkylations or cleavage of the peptide backbone by carbonyl addition occur only at higher temperatures and/or with prolonged reaction times (see **14** and **15** in *Scheme 4*). Very little or no epimerization of stereogenic centers occurs under the conditions employed. Possible reasons for the feasibility of these surprizing conversions of CS are discussed (*Schemes 4* and *5* and *Fig. 3*). For comparison, [MeAla[3]]CS (**2b**) and [D-MeAla[3]]CS (**2a**) were also prepared by conventional peptide synthesis in solution (*Schemes 6* and *7*). Their ^1H- and ^{13}C-NMR spectra are compared with those of CS (*Table 2* in the *Exper. Part*).

1. Introduction – The Start of a New Research Project. – In two previous papers, we demonstrated that it is possible to generate polylithiated derivatives of linear [1] and of cyclic peptides [2] containing sarcosine Li enolates, and thus to introduce side chains into a given peptide[6]). Here we describe the application of this procedure to the immunosuppressive cyclic undecapeptide cyclosporin A (CS)[1])[7]) containing a sarcosine residue (Sar: $MeNHCH_2COOH$) at position 3. This sequence of publications is in fact a reversal of the course of events, because the first peptide which we actually submitted to polylithiation

[1]) Cyclosporine (CS) is defined as the cyclosporin-A structure to facilitate nomenclature of other cyclosporine derivatives. Thus, cyclosporin C becomes [2-(L-threonine)]cyclosporine and is abbreviated [Thr[2]]CS. This convention avoids the use of the alphabet for specification of cyclosporine derivatives (see below, references to previous work on CS).

[2]) Postdoctoral research at ETH-Zürich 1987–1989, financed by *Sandoz AG*, Basel.

[3]) *National Institute of Health* postdoctoral associate, ETH-Zürich, 1983/84.

[4]) *Swiss National Science Foundation* postdoctoral fellowship (project No. 2.093.-0.86), ETH-Zürich, 1984–1986.

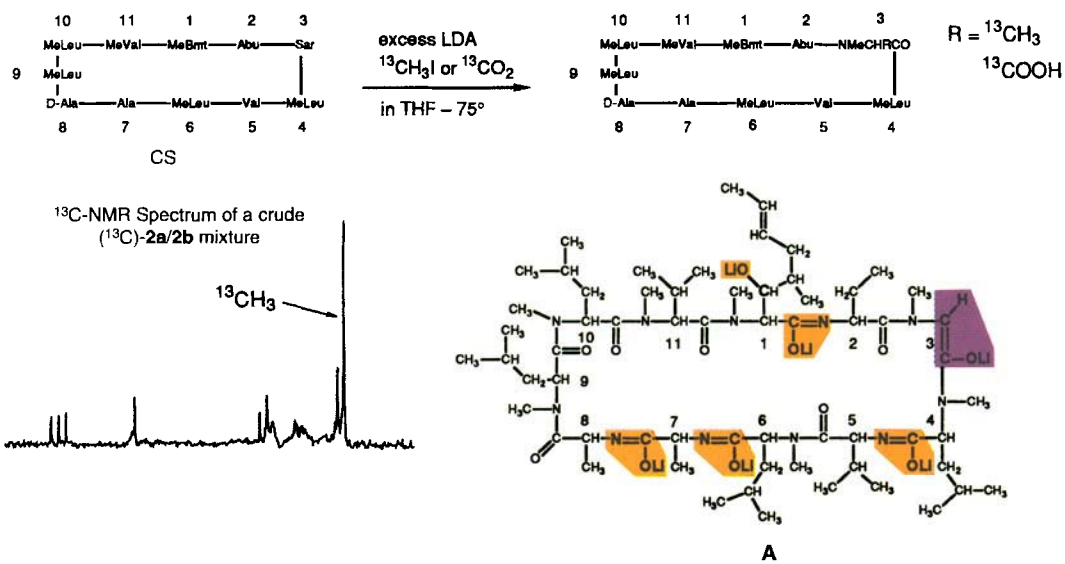
[5]) Part of the Dissertation of *A. T.*, No. 9454, ETH-Zürich, 1991.

[6]) For a review article about our endeavours into the chemistry of peptides using nonconventional methods, see [3]. Some of the results described here were mentioned in [4].

[7]) Other cyclosporines [5] were modified in the same way [6].

and subsequent reaction with an electrophile was CS. One day in the fall of 1983, one of us returned to Zürich from a consulting visit in Basel with a sample of cyclosporin A which was given to him jokingly after the proposal was forwarded that it might be possible to generate an enolate of this highly lipophilic undecapeptide which contains seven *N*-methyl-amino acids and four non-methylated ones (besides the four rather acidic CO–NH protons, there is an OH group in MeBmt, the amino-acid residue 1, unique to the cyclosporins, which would all have to be deprotonated before a sarcosine enolate in the subunit Abu-Sar-MeLeu could form with excess base). The next day, we tried an alkylation with $^{13}CH_3I$ and detected the desired product by ^{13}C-NMR spectroscopy from an intensive new signal in the complex aliphatic region of the spectrum of CS. Indeed, the very-poor-quality product spectrum indicated that an Abu-MeAla-MeLeu unit had been formed with one of the diastereoisomers prevailing (*Scheme 1*). Comparison with inde-

Scheme 1



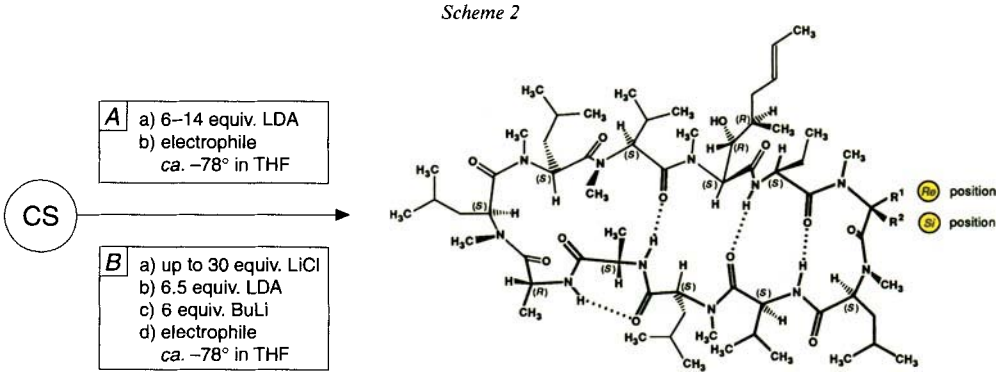
pendently synthesized authentic samples (see below, *Chapt. 4*) proved the major product to have a D-MeAla residue. Thus, we had indeed generated the hexalithio derivative **A**[8]) (see *Scheme 1*). Over the years, numerous reactions of various cyclosporines involving strong Li bases were carried out in the *Sandoz* laboratories and at ETH [6], and we have learned some rules which led to successful *C*-alkylations of other, less complex peptides [1] [2].

The main purpose of the present publication is to describe a few study cases with full experimental detail, some mechanistic investigations, and independent syntheses of [MeAla^3]CS^1) (**2b**) and [D-MeAla^3]CS^1) (**2a**).

[8]) We do not know the configuration around the enolate C=C and the azaenolate C=N bonds of **A**. Broad and unresolved ^{1}H-NMR signals observed with solutions of **A** in (D_8)THF did not lend themselves for deducing any structural information. See, however, *Chapt. 3* and *Fig. 3* below.

2. Results. – CS is very soluble in organic solvents – and almost insoluble in H_2O. Upon addition of LDA to a THF solution of CS at dry-ice temperature, a heterogeneous or a gelatinous mixture usually begins to form above *ca.* 4 equiv. of base. If addition of LDA is continued above the 6 equiv. required for the formation of **A** (*Scheme 1*), the mixture turns homogeneous and stirrable again[9]) (*Conditions A* in *Scheme 2*). Excess strong Li base can also be supplied by adding BuLi to a mixture obtained with *ca.* 6 equiv. of LDA, with the extra benefit that the potential proton source $(i\text{-Pr})_2NH$ [7] is removed. Instead of excess LDA, LiCl can be used to solubilize the hexalithio derivative **A**. It turns out that CS/LiCl mixtures are soluble in THF at −75° with up to 30 equiv. of LiCl and that CS, like other peptides, are actually solubilizing LiCl in this solvent [8]. No precipitates are formed when the CS/LiCl solutions are combined with LDA (and BuLi), which corresponds to *Conditions B* in *Scheme 2*. The hexalithio-CS species present under the two

Scheme 2



Conditions A: major diastereoisomer of type **a**, $R^2 = H$
Conditions B: major diastereoisomer of type **b**, $R^1 = H$

	R^1	R^2		R^1	R^2
CS	H	H	**7a**	CH_2OH	H
1	H	D	**8a**	CH_2OCOPh[b])	H
2a	Me	H	**9a**	$CH_2OCOCHN_2$[b])	H
b	H	Me	**10a**	CO_2H[c])	H
3a	$CH_2CH{=}CH_2$	H	**11a**	CO_2Me[d])	H
b	H	$CH_2CH{=}CH_2$	**12a**	MeS	H
4a	$CH_2C{\equiv}CH$	H	**b**	H	MeS
5a	$CH_2CO_2(t\text{-Bu})$[a])	H	**13a**	4-TolS	H
b	H	$CH_2CO_2(t\text{-Bu})$[a])	**b**	H	4-TolS
6a	CH_2Ph	H			

[a]) Free acid and methyl ester by cleavage (CF_3CO_2H) and esterification (CH_2N_2), see *Exper. Part*, procedures following that for the preparation of **5a**/**b**.
[b]) From **7a** and the corresponding acyl chlorides.
[c]) With $^{13}CO_2$, the labelled acid was obtained.
[d]) From the acid **10a** and CH_2N_2 or by methoxycarbonylation.

[9]) This is attributed to breaking up $(Li_6CS)_n$ aggregates by formation of mixed aggregates with the added LiX ($LiNR_2$ or LiCl in this work), with an added-salt effect on the solvent properties of THF [1] [2] [4]; see also discussion and [8] below.

sets of *Conditions A* and *B* are different, one giving rise to preferential formation with electrophiles of the diastereoisomers of type **a**, the other one of type **b**, *i.e.* to overall substitution of H^{Re} or of H^{Si}, respectively, at the sarcosine CH_2 group (*Scheme 2*). The yields can be as high as 90%, and the selectivities may exceed a 5:1 ratio (for specific values, see *Exper. Part*). The *Si*-selectivity observed in the presence of LiCl is normally higher than the *Re*-selectivity in its absence. Typical products **1**–**13** are listed in *Scheme 2*, some more examples are given in the *Exper. Part* (*Table 1*).

The diastereoisomers of type **a** and **b** can be separated by chromatography. Even the tiny Me group (only 14 atomic mass units added!) causes a mixture **2a**/**2b** of CS derivatives (M_r 1216), to give in presence of CS three spots on a TLC plate under appropriate conditions. The configurational assignment of the products to the **a** or **b** series follows from comparison with authentic samples of the methylation products **2a** and **2b** (see *Chapt. 4*) and from NMR data. There is a very characteristic difference between the two series: the NMR spectra of the diastereoisomers **a** (new substituent in *Re* position, newly created D-amino-acid residue) usually resemble the spectrum of CS over wide ranges; the NMR spectra of the epimers **b** (new substituent in *Si*-position, L-amino-acid residue) are quite different and often show the presence of several conformers. This is not surprising if one considers that sarcosine is part of a β-II′ turn (at least in organic solvents and in the crystal structure), placing H^{Re} in a *quasi*equatorial, H^{Si} in a *quasi*axial position. As can be

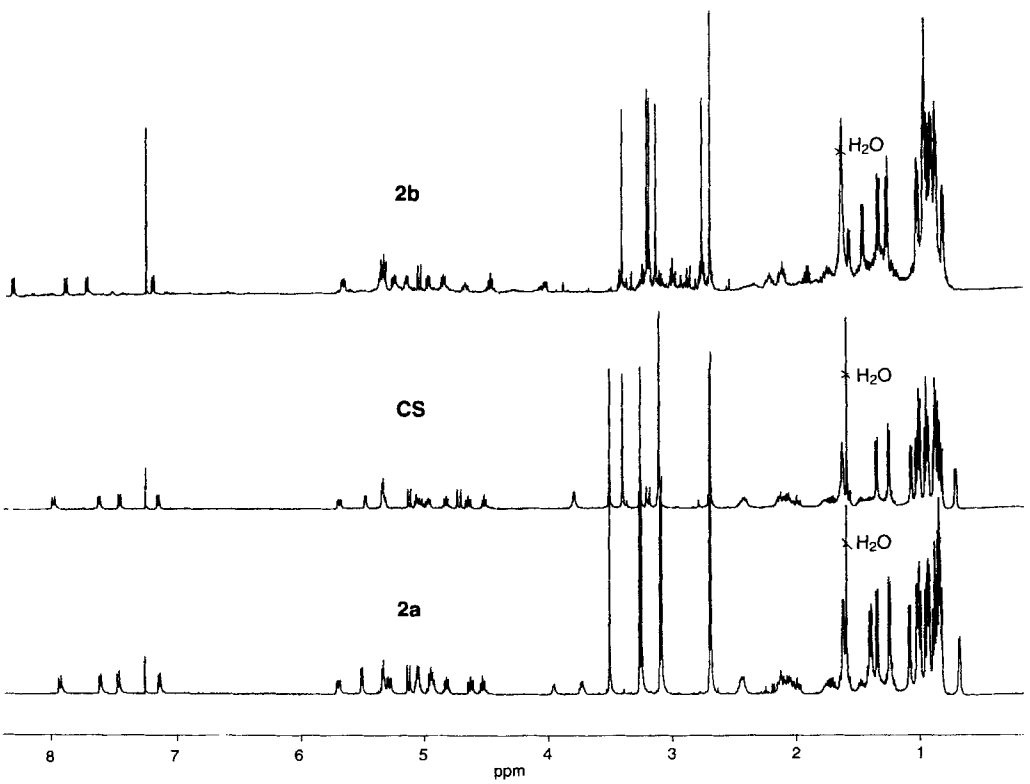


Fig. 1. *520-MHz ^{1}H-NMR Spectra* ($CDCl_3$) *of [*D*-MeAla^3]CS* (**2a**), *CS, and [MeAla^3]CS* (**2b**)

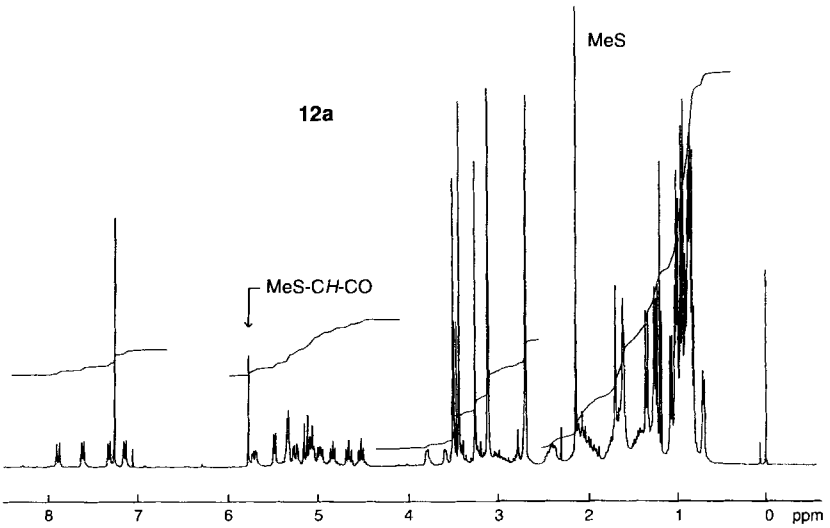


Fig. 2. *300-MHz ^{1}H-NMR* ($CDCl_3$) *Spectrum of the methylthio derivative* **12a**

seen by inspection of the *Formula* in *Scheme 2*[10]), a larger substituent in the *Re*-position does not encounter severe steric interactions, so that the turn structure is preserved. Substituents in the *Si* position on residue 3, however, would be in a 1,3-coplanar disposition with the Me–N group of MeLeu, so that $A^{1,3}$ strain [10] will force the β-II′ turn to change to either a β'- or a *cis*-β turn[11]). This causes major structural disruptions which show up in the NMR spectra of the diastereoisomers **b** (see *Figs. 1* and *2*).

3. Discussion and Mechanistic Studies. – There are several surprising aspects of the results described in *Chapt. 2*, concerning both the reactivity of CS and the stereoselectivity of the reactions with strong base and electrophiles.

It is easy to envisage problems which could have prevented the observed transformation: *i*) The Li-alkoxide group on MeBmt could be alkylated to an ether. *ii*) The Li azaenolates[12]) (**B** in *Scheme 3*) could be *N*-alkylated (*O*-alkylation would not be harmful). *iii*) While stereogenic centers adjacent to azaenolate units would be somewhat protected against deprotonation (see **C**) and subsequent epimer formation (centers of residues 1, 2, and 4–8, see **A** in *Scheme 1*), those of the amino-acid residues 9–11 are not subject to this effect (see **D** in *Scheme 3*). *iv*) In one of the procedures given in *Scheme 2*, we add BuLi to the reaction mixture which could lead to nucleophilic addition with cleavage of the peptide backbone, *i.e.* ring opening of the CS macrocycle.

N-Alkylation turns out to be a competing process only at elevated temperatures (the desired conversion is normally carried out at −75° with excess RX). With 2 equiv. only of

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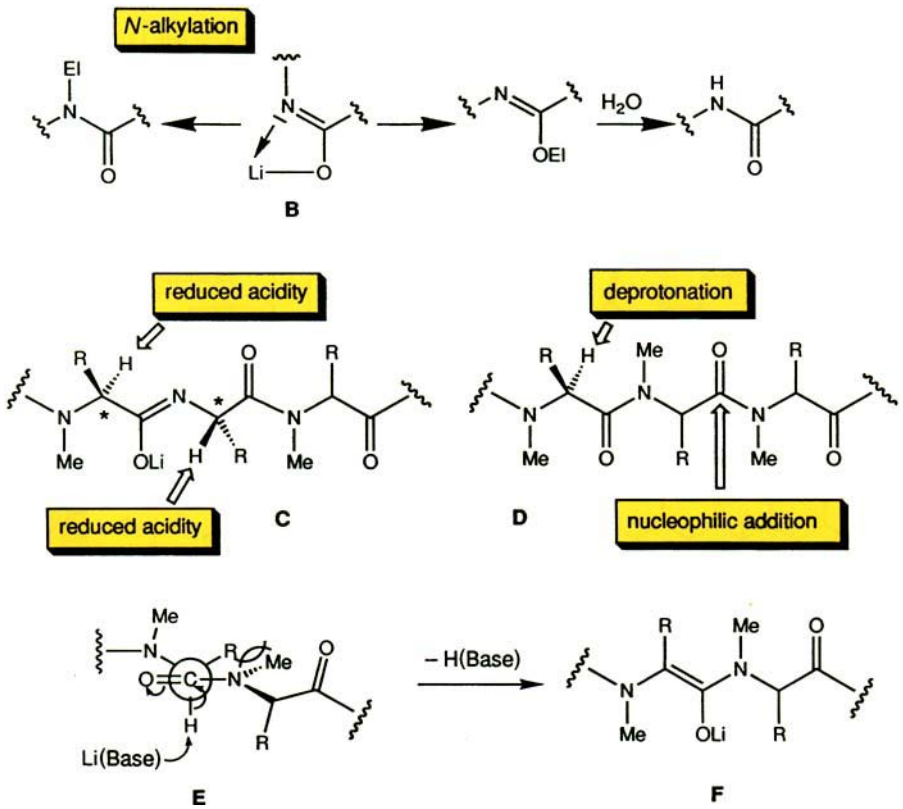
[10]) This *Formula* closely resembles the crystal structure of CS which, with the exception of the position of the MeBmt side chain, is essentially identical to the NMR structure in non-polar solvents [9a, b]. One of the conformers of ($^1\Psi^2$, CS-N)CS was found to be essentially identical to that of CS in $CDCl_3$ [9]. For a conformational NMR analysis of CS in $CDCl_3/CD_3OD$, CD_3OD to 50% CD_3OD in D_2O, see [9d].

[11]) In the review article [4] (Fig. 26), space-filling models of the turn sections with D- and L-MeAla are shown.

[12]) For crystal and solution structures of Li azaenolates (X-ray and NMR experiments), see [11].

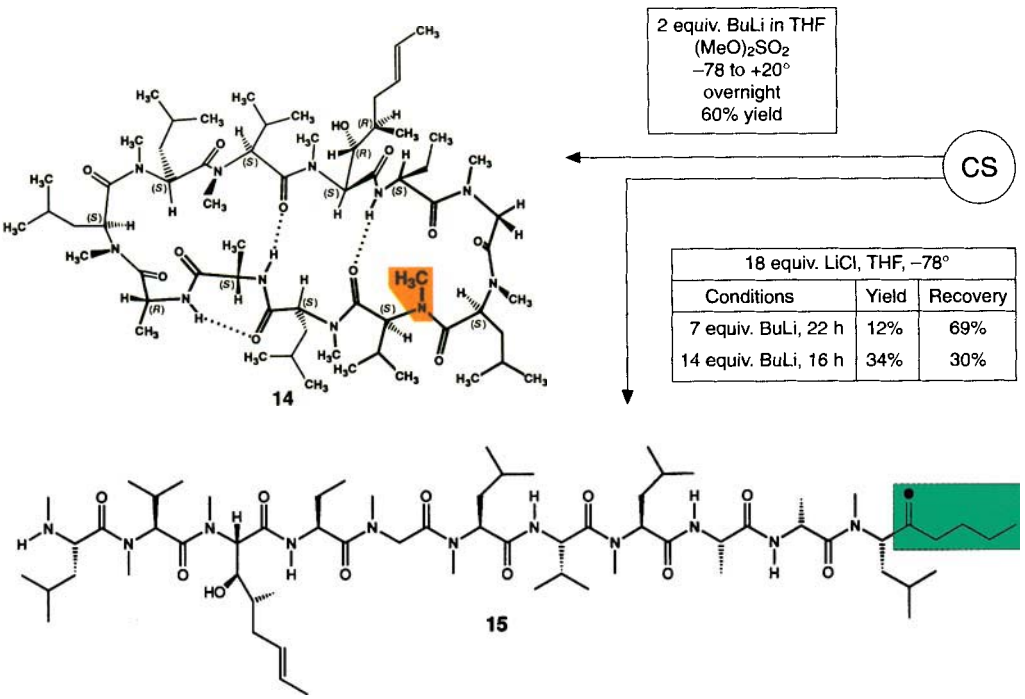
Scheme 3



base, dimethyl sulfate as reagent, and temperatures up to +20°, CS can be *N*-methylated regioselectively to [MeVal[5]]CS (**14**; *Scheme 4*). Enolate formation from an α-branched *N*,*N*-disubstituted amide is intrinsically difficult (see **E** → **F** in *Scheme 3*). It requires the amide to adopt a conformation **E** with the H-atom to be removed perpendicular to the amide plane. This conformation is severely destabilized by $A^{1,3}$ strain [10c] between substituents on the amide N-atom and on C(α) (see **E**)[13]). Therefore, it is probably not too unexpected that epimerization and/or *C*-alkylation with formation of an α,α-disubstituted amino-acid residue at positions 9–11 of CS are hardly observed. Under the conditions described in this paper, less than 5% of products arising by such processes were occasionally isolated from certain chromatography fractions and characterized. On the other hand, treatment of a CS THF solution with *t*-BuOLi at 50° gives selectively [D-MeLeu[10]]CS, the structure of which was proved by total synthesis [9e]. Finally, ring opening is observed only under the most brutal conditions: stirring a solution obtained from CS, 18 equiv. of LiCl, and 7–14 equiv. of BuLi in THF at dry-ice temperature for up

[13]) Once the enolate **F** (*Scheme 3*) is formed, the former amide C–N bond becomes an enamine C–N bond, with a low barrier to rotation and different conformational preferences [7] [12] [13]. **F** is actually at the same time a Li enolate and an ene-diamine, a highly electron-rich system!

Scheme 4



to one day leads, after aqueous workup, to the isolation of the open-chain peptide **15** with a butyl-ketone unit at the C-terminus[14]).

It is difficult to make reasonable comments on the observed stereochemical course of the reactions – newly introduced substituent in the *Re*-position with excess LDA, in the *Si*-position with LDA/BuLi/LiCl. The most simple case is the replacement of H by D at the sarcosine CH_2 group, and the conditions leading to the more selective reaction are those using LiCl in THF (→**1**; see *Scheme 2*). We chose this transformation to find out, which proton, H^{Re} or H^{Si}, is abstracted (see *Scheme 5*; the (*Z*)-configuration of the CS enolates is arbitrary). Thus, CS is deprotonated under the *Conditions B* and the resulting solution quenched with MeOD or CD_3CO_2D/MeOD 1:1. The product analysis is simple because the two diastereoisotopic H-atoms have very different chemical shifts (H^{Re} at 3.23, H^{Si} at 4.76 ppm) [9b] and shows that the *Si* position is up to 85% deuterated (product **1**; see *Scheme 5a*). The material thus obtained is subjected to the very same conditions under which it was formed, but the lithiated CS is now quenched with proton acid. The result is that most of the D is lost (→ CS; *Scheme 5a*). The outcome of this reaction cycle proves unequivocally that the stereochemical course of the exchange is a substitution with retention (definition see [14]).

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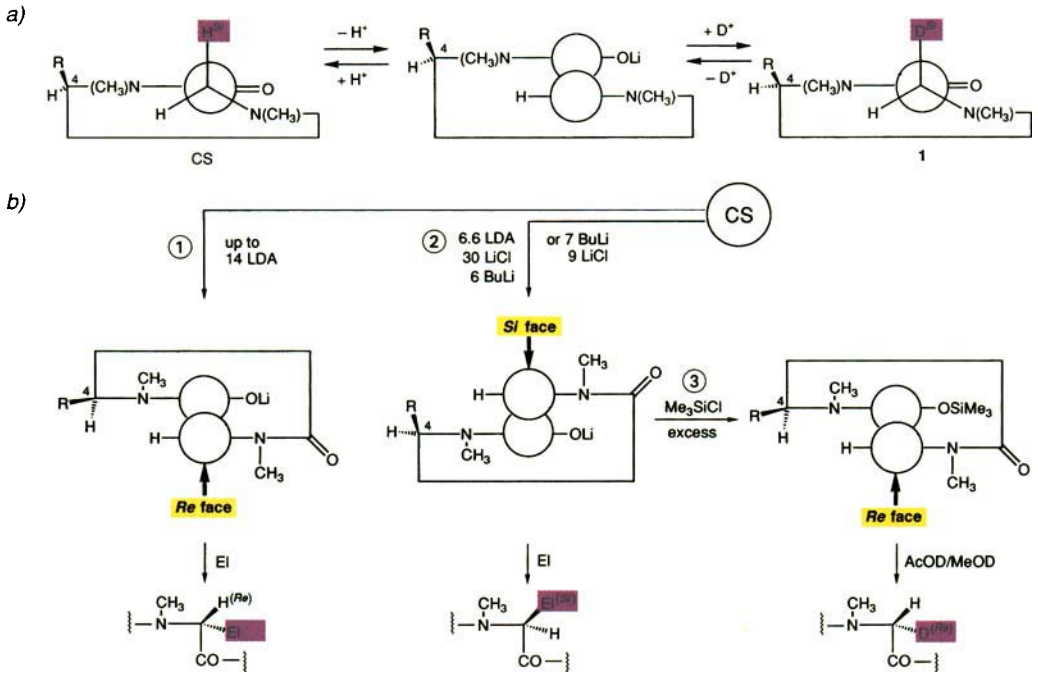
[14]) Similarly, the reaction of CS with 14 equiv. of *t*-BuLi in the presence of 18 equiv. of LiCl in THF (–75°, 16 h; then quenching with aqueous HCl solution) gave, in 10% yield after chromatography (FC, 10% MeOH in Et_2O; 40% CS recovered), the *t*-Bu ketone H-MeLeu-MeVal-MeBmt-Abu-Sar-MeLeu-Val-MeLeu-Ala-D-Ala-MeLeu-^{t}Bu ($[\alpha]_D^{r.t.} = -156.8$ ($c = 1.35$, $CHCl_3$)) which was fully characterized by ^{1}H- and ^{13}C-NMR and by mass spectroscopy.

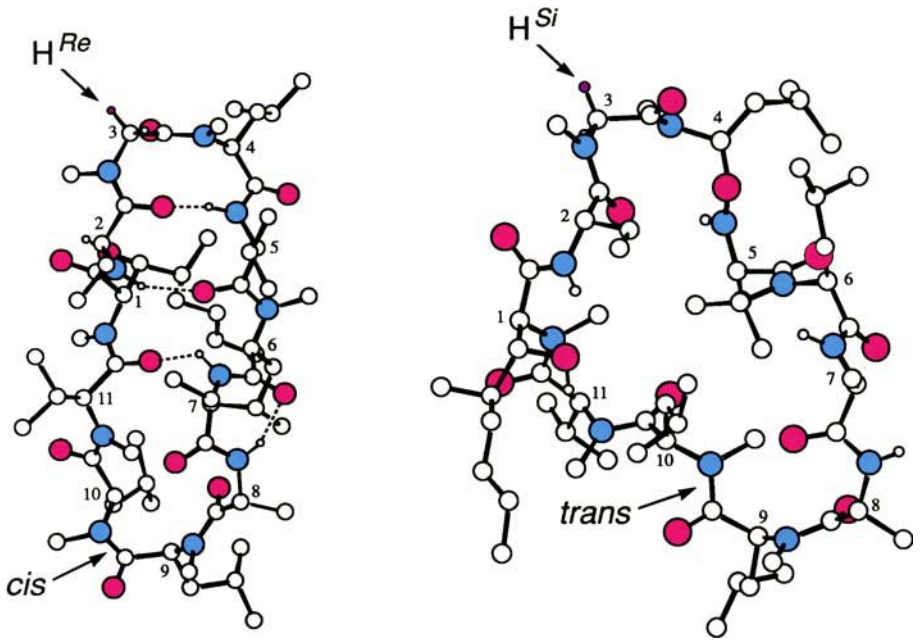
Scheme 5



Deuteration of the sarcosine unit of CS is performed in yet another way: the hexalithio derivative generated in the presence of LiCl (either with LDA/BuLi or with BuLi alone) is treated with excess Me_3SiCl and the resulting silyl derivative quenched with AcOD/MeOD (see ② and ③ in *Scheme 5b*). This leads to introduction of D-atom in the *Re*-position, a reversal of the stereochemical course of reaction as compared to the parent Li derivative.

In summary, the structure of the enolate formed with LDA alone is such that the *Re* face of the trigonal center on the double bond is more readily available for electrophilic attack (see ① in *Scheme 5b*), the enolate generated in the presence of LiCl reacts preferentially from the *Si*-face (see ②), and the corresponding polysilylated compound again from the *Re*-face (see ③).

Considering the complexity of hexalithio-CS, containing one LiOR group, four Li-azaenolate units [11] and a Li-enolate moiety [4], it is impossible to propose detailed structures and mechanisms rationalizing the observed results. We can, however, not resist to draw attention to a striking relationship between the solution structures of CS itself and the relative topicities [15] of the transformations described above (*Fig. 3*). In $CDCl_3$ and (D_8)THF, CS is known to have a conformation [9b] with the $C-H^{Re}$ bond of the sarcosine moiety in approximately the right position to be abstracted by base according to the stereoelectronic rules [17] (→ (*Z*)-enolate; *cf. Scheme 3*, **E**); the *Re*-face of the corresponding enolate is the one from which electrophilic attack occurs preferentially when the enolate is generated with LDA in THF solution. In (D_8)THF/LiCl, the confor-



Cyclosporin A in $CDCl_3$
- 9,10-*cis* peptide bond
- 4 intramolecular NH···O=C

very similar to crystal structure [9a]

[Cyclosporin A + 30 LiCl] in $(D_8)THF$
- no *cis* peptide bond
- no intramolecular NH···O=C

Fig. 3. *Solution structures of CS as determined by NMR spectroscopy* [9b] [16]

mation of CS[15]) is such [16] that the C–H^{Si} bond of sarcosine is perpendicular to the amide carbonyl plane (→ (*Z*)-enolate as well!); it is the *Si*-face on which reactions of the enolate occur selectively when a LiCl-containing THF solution of CS is used for the deprotonation. If we presume that the room-temperature NMR conformations of CS in the two different solvent systems are preserved upon cooling to −75°, and that – independent of the sequence of events during deprotonation[16]) – the macrocyclic ring keeps blocking the face on which it is located in the original conformation, we have a speculative[16]) interpretation of the reverse stereochemical course of the reactions in salt-free and LiCl-containing solutions.

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[15]) *Cf.* the conformation of CS bonded to cyclophilin [18a] and to an antibody immunoglobulin [18b]. See also the dramatic changes occurring in the NMR spectra of CS in the presence of Na^+, Mg^{2+}, and Ca^{2+} [18c].

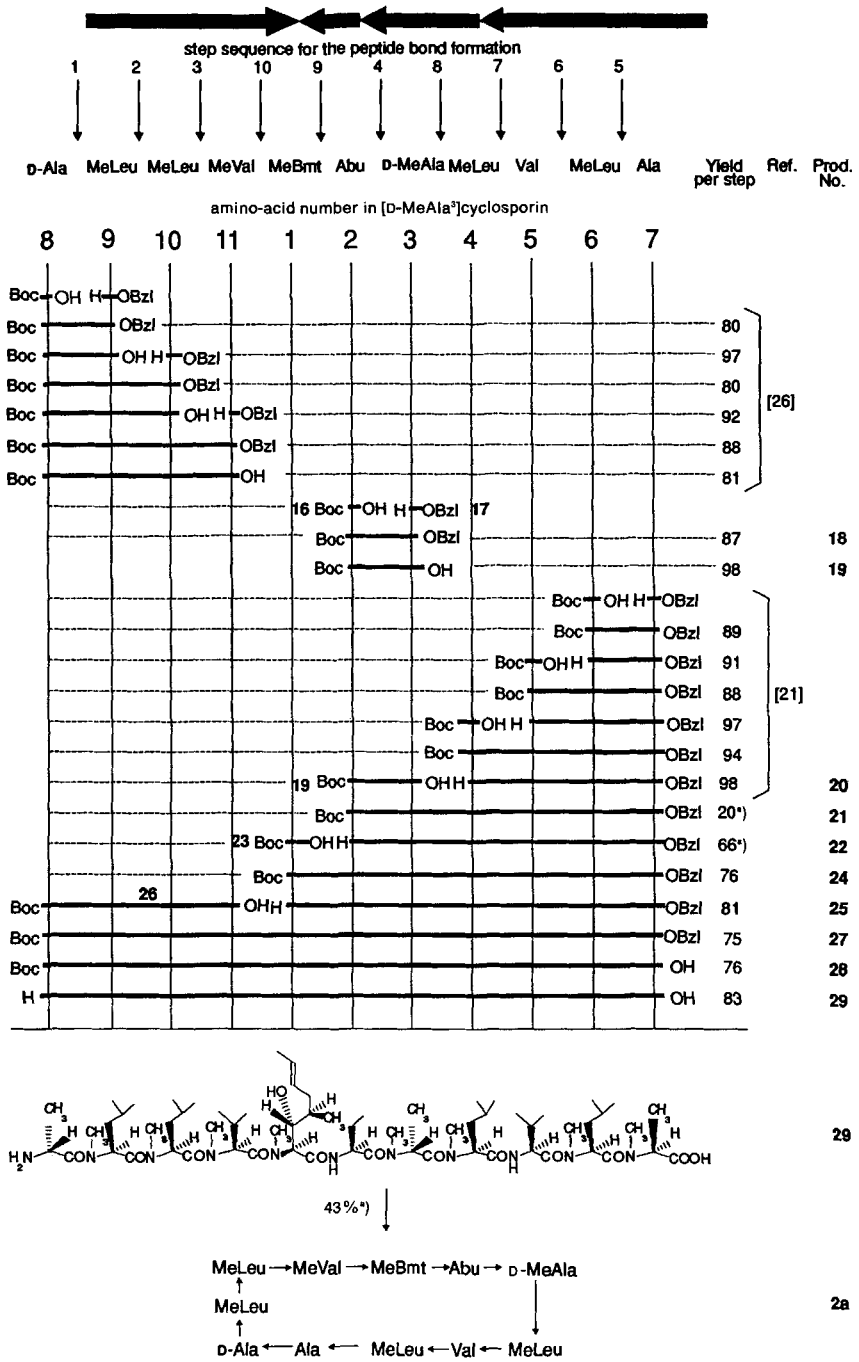
[16]) If the rate of deprotonation correlates with the acidity of the protons involved (*Brønsted* correlation; kinetic *vs.* thermodynamic acidity [19]), the MeBmt OH group of CS should be deprotonated first, followed by the four NH groups, and the sarcosine CH_2 group last. It is impossible to know which conformational and configurational changes occur before H^{Re} or H^{Si} of sarcosine is abstracted. According to *Hauser*'s rule (site of last deprotonation is most reactive! [20]), the enolate C-atom of Li_6CS (**A** in *Scheme 1*) should react with electrophiles first.

4. Independent Synthesis of [D-MeAla³]CS (2a) and of [MeAla³]CS (2b). – The synthesis of [D-MeAla³]CS (**2a**) is outlined in *Scheme 6*. The same fragment-condensation technique was used as for the synthesis of cyclosporine [21]. H-MeLeu-Val-MeLeu-Ala-OBzl (**20**) was condensed with Boc-Abu-D-MeAla-OH (**19**; obtained from **16** and **17** *via* **18**) using the mixed pivalic-anhydride method (**19** replaces Boc-Abu-Sar-OH, the corresponding intermediate in the CS synthesis [21a]). Boc-Abu-D-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**21**) was *N*-deprotected with CF_3COOH at −20°, then H-Abu-D-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**22**) was condensed with Boc-MeBmt-OH (**23**) using the dicyclohexylcarbodiimide (DCCl) coupling method in the presence of 1*H*-benzotriazol-1-ol (BtOH) [22] (→ **24**). After removal of the Boc-protecting group, the resulting heptapeptide H-MeBmt-Abu-D-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**25**) was condensed with Boc-D-Ala-MeLeu-MeLeu-MeVal-OH (**26**) with the aid of the reagent (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate ($(BtO)P(Me_2N)_3^+PF_6^-$, *Castro*'s reagent) [23] in the presence of *N*-methylmorpholine in CH_2Cl_2. The ester group of the undecapeptide Boc-D-Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu-D-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**27**) was removed by hydrolysis with 0.2N NaOH in EtOH at 0° (→ **28**) and the Boc group with CF_3COOH at −20° (→ **29**). The unprotected undecapeptide **29** was then cyclized in CH_2Cl_2 (0.0002M) using 4 equiv. of propylphosphonic anhydride ($(PrPO_2)_n$) [24], and 5 equiv. of 4-(dimethylamino)pyridine (1 day at room temperature) to yield crystalline [D-MeAla³]cyclosporine (**2a**), isolated in 43% yield.

The synthesis of [MeAla³]CS (**2b**) as described in *Scheme 7* was carried out by a similar fragment-condensation technique as that used for the epimer **2a**. To avoid epimerization of the activated peptide Boc-Abu-MeAla-OH (epimer of **19**) during condensation with the tetrapeptide H-MeLeu-Val-MeLeu-Ala-OBzl (**20**; also used for the construction of **2a**), the corresponding amino acids were added step by step to this tetrapeptide **20**. Thus, Boc-MeAla-OH (**30**) was condensed with **20** using the mixed pivalic-anhydride method as reported by *Zaoral* [25] and adapted by one of us for *N*-methyl-amino-acid derivatives [26]. Boc-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**31**) was thus isolated in 83% yield. After removal of the Boc group with CF_3COOH at −20°, the resulting pentapeptide ester **32** was condensed with Boc-Abu-OH (**16**) using the same technique (yield: 73%). The hexapeptide Boc-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**33**) was *N*-deprotected with CF_3COOH at −20°, and then **34** was condensed with *N,O*-isopropylidene-MeBmt-OH (**35**) using the DCCl method as for the synthesis of epimer **2a**. The isopropylidene protecting group was removed from the heptapeptide **36** with 1N HCl in MeOH, and the acid neutralized with $NaHCO_3$. The final amide bond to produce the undecapeptide Boc-D-Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl (**38**) was closed by coupling Boc-D-Ala-MeLeu-MeLeu-MeVal-OH (**26**) with the heptapeptide **37**, using *Castro*'s reagent. The ester group of **38** was removed by hydrolysis with 0.2N NaOH in EtOH at 0° (→ **39**), and the Boc group by treatment with CF_3COOH at −20° (→ **40**). The unprotected undecapeptide **40** was cyclized as described for **2a** giving [MeAla³]CS (**2b**; not crystalline) in 42% yield.

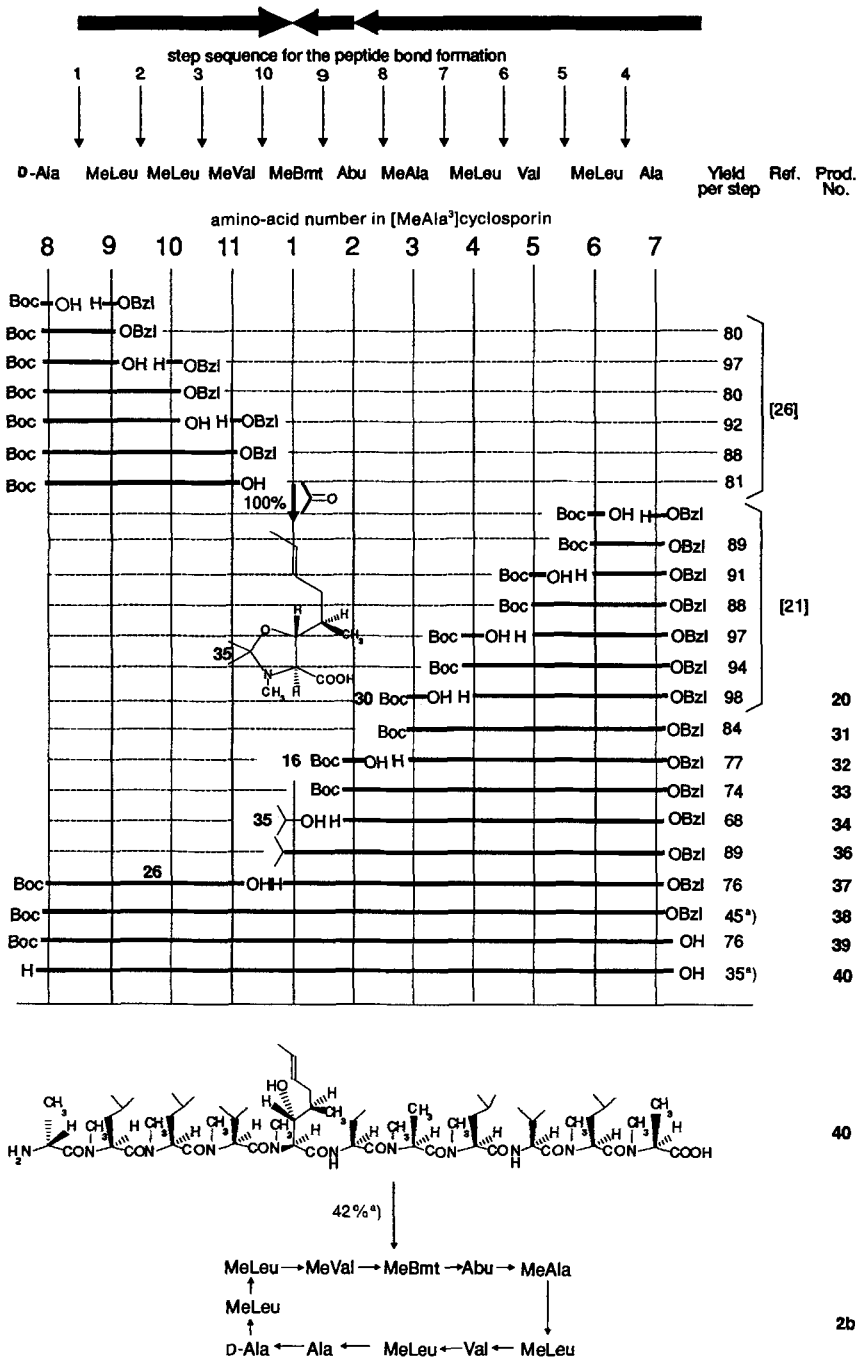
The samples of the epimers **2a** and **2b** obtained by the syntheses were identical by ^{1}H-NMR comparison with those isolated from methylation of CS as described in *Chapt. 2*. Comparing the systematic synthesis of the two CS derivatives **2a** and **2b** from the component amino acids, needed for structure proof, with the preparation of the same

Scheme 6. *Synthetic Route Leading to [D-MeAla³]CS* (**2a**) *from the Amino-Acid Components*



[a]) Yield not optimized.

Scheme 7. *Synthetic Route Leading to [MeAla³]CS* (**2b**) *from the Amino-Acid Components*



a) Yield not optimized.

compounds by the one-step methylation of readily available CS demonstrates the obvious advantage which the direct modification of a peptide may constitute.

Experimental Part

1. *General.* THF was freshly distilled from K under Ar. TLC: *Merck* silica gel *60* F_{254} anal. plates. LC: *Merck* silica gel *60* (40–63 μm, 230–400 mesh). Optical rotations: *Perkin-Elmer 241* polarimeter. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AMX-400* (400 MHz), *Bruker-WH-360* (360 MHz), *Bruker-WM-300* (300 and 75 MHz, resp.), *Varian-FT-80A* (80 and 20 MHz, resp.) instruments; for atom numbering, the amino-acid residue number (obtained by numbering residues from the N-terminus) follows the atom number of each amino-acid residue (starting from the original COOH group), *e.g.* in H-D-Ala-MeLeu-MeLeu-MeVal-OH, H–C(2.1) is H–C(2) (= H–C(α)) of the D-alanine residue, Me–C(3.4) is 1 Me–C(3) of the MeVal residue, and Me–N(2.4) is MeN of the valine residue (in CS, MeBmt is residue 1 and MeVal residue 11; see also [26]).

2. *General Procedure for the Alkylation of CS. Method A:* A soln. of $(i\text{-Pr})_2$NH in THF under Ar was cooled to – 78° and then treated with BuLi in hexane and stirred for 30 min. To the resulting LDA soln., CS in THF, and after stirring for 1 h, the electrophile were added.

Method B: To a soln. of $(i\text{-Pr})_2$NH in THF under Ar, BuLi in hexane was added at 0°. After 20 min of stirring at 0°, this soln. was cooled to – 78°. Separately, a soln. of CS and eventually dry LiCl in THF was prepared under Ar and cooled to – 78°. The LDA soln. was transferred to the CS soln. After 2 h of stirring, BuLi and the appropriate electrophile were added.

3. *Alkylations. [(2-^{2}H)Sar^3]CS* (**1**). According to *Method B*, 10 ml of THF, 0.95 ml (6.70 mmol) of $(i\text{-Pr})_2$NH, 4.3 ml (6.70 mmol) of BuLi, a soln. of 1.23 g (1.02 mmol) of CS and 383 mg (9.04 mmol) of LiCl in 20 ml of THF, 4.3 ml (6.70 mmol) of BuLi, and 2 ml of MeOD were used. The soln. was warmed to r.t., and 2 ml of AcOD and Et_2O were added. The org. layer was washed with sat. $NaHCO_3$ and sat. NaCl soln. All aq. layers were additionally extracted twice with Et_2O. The combined org. layers were dried ($MgSO_4$) and evaporated. Purification by LC (Et_2O/i-PrOH 94:6) gave 1.17 g (95%) of **1**. ^{1}H-NMR: 82% of [(2-$^2H^{Si}$)Sar^3]CS and 18% of [(2-$^2H^{Re}$)Sar^3]CS. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.71 (*d*, *J* = 6, Me–C(4.1)); 0.80–1.12 (*m*, Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.28 (*d*, *J* = 6, Me–C(2.8)); 1.38 (*d*, *J* = 6, Me–C(2.7)); 1.40, 1.70, 2.10 (3*m*, H–C(4.1), H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6), 2 H–C(3.9), H–C(4.9), 2 H–C(3.10), H–C(4.10), H–C(3.11)); 1.64 (*d*, *J* = 3, Me–C(7.1)); 2.43 (2*m*, H–C(5.1), H–C(3.5)); 2.69 (*s*, Me–N(2.10)); 2.71 (*s*, Me–N(2.11)); 3.11 (*s*, Me–N(2.4)); 3.12 (*s*, Me–N(2.9)); 3.18 (*s*, H–C(2.3) and a small *d* of CS); 3.27 (*s*, Me–N(2.6)); 3.40 (*s*, Me–N(2.3)); 3.51 (*s*, Me–N(2.1)); 3.83 (br. *s*, H–C(3.1), OH–C(3.1)); 4.53 (*m*, H–C(2.7)); 4.65 (*t*, *J* = 9, H–C(2.5)); 4.74 (*s* and *d*, *J* = 14, *ca.* 0.2 H, H–C(2.3) of [(2-$^2H^{Re}$)Sar^3]CS and CS); 4.83 (*m*, H–C(2.8)); 5.01 (*m*, H–C(2.2), H–C(2.6)); 5.10 (*m*, H–C(2.10)); 5.13 (*d*, *J* = 12, H–C(2.11)); 5.35 (*m*, H–C(6.1), H–C(7.1), H–C(2.4)); 5.50 (*d*, *J* = 5, H–C(2.1)); 5.71 (*dd*, *J* = 12, 4, H–C(2.9)); 7.16 (*d*, *J* = 8, H–N(2.8)); 7.47 (*d*, *J* = 8, H–N(2.5)); 7.64 (*d*, *J* = 8, H–N(2.7)); 7.98 (*d*, *J* = 10, H–N(2.2)).

[D-MeAla^3]CS (**2a**). According to *Method A*, 480 ml of THF, 6.96 ml (49.2 mmol) of $(i\text{-Pr})_2$NH, 33.5 ml (44.5 mmol) of BuLi, 8 g (6.64 mmol) of CS in 120 ml of THF, and 2.06 ml (33.1 mmol) of MeI were used. Within 1.5 h the mixture was warmed to r.t. Then 40 ml of H_2O were added, and the solvent was evaporated. The residue was taken up in Et_2O and H_2O. The org. layer was washed 4 times with half-sat. NaCl soln., dried ($MgSO_4$), and evaporated. LC (1200 g of silica gel, AcOEt sat. with H_2O) gave 3.4 g of product which was not pure. After a second LC (200 g of silica gel, Et_2O/dimethoxyethane 95:5), 2.1 g (26%) of **2a** were isolated. $[\alpha]_D^{20} = -209$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): identical with that of [D-MeAla^3]CS of the total synthesis.

[MeAla^3]CS (**2b**). According to *Method B*, 7.5 ml of THF, 0.47 ml (3.3 mmol) of $(i\text{-Pr})_2$NH, 3.3 mmol of BuLi, a soln. of 640 mg (15 mmol) of LiCl and 601 mg (0.5 mmol) of CS in 12 ml of THF, 3 mmol of BuLi, and 20 equiv. of MeI were used. The mixture was stirred for 3.5 h at – 23°, then warmed up to r.t. and quenched with aq. NH_4Cl soln. The aq. soln. was extracted 3 times with Et_2O and the combined org. layer washed with a half-sat. NaCl soln. several times and dried (Na_2SO_4). After evaporation, the crude product was purified by LC (silica gel, Et_2O/MeOH 100:5): 559 mg (92%) of **2a**/**2b** 1:5. ^{1}H-NMR ($CDCl_3$, 200 MHz): nearly identical with that of [MeAla^3]CS of the total synthesis.

[D-2-(Methylamino)pent-4-enoyl^3]CS (= [D-MeNva(4,5-didehydro)^3]CS; **3a**). A cooled (– 75°) THF soln. (50 ml) of 1 g (0.83 mmol) of CS was treated with 15 equiv. of LDA soln. The resulting clear soln. was stirred for 1 h at – 75°, and then 3.6 ml (42.6 mmol) of allyl bromide were added. The mixture was allowed to warm to r.t. and

stirred for additional 2 h, followed by quenching with 10 ml of H_2O. After evaporation of the THF, the aq. phase was extracted with Et_2O. The org. phase was dried ($MgSO_4$), evaporated, and chromatographed (silica gel, Et_2O/MeOH 96:4) to give 204 mg (19%) of **3a** (containing some doubly allylated product). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.68–1.4 (*m*, 49 H); 1.5–2.5 (*m*, 13 H); 2.6 (*t*, *J* = 3, 2 H); 2.68 (*s*, 3 H); 2.69 (*s*, 3 H); 3.07 (*s*, 3 H); 3.10 (*s*, 3 H); 3.25 (*s*, 3 H); 3.26 (*s*, 3 H); 3.50 (*s*, 3 H); 3.74 (br. *s*, 1 H); 4.5–5.76 (*m*, 14 H); 7.14 (*d*, *J* = 8, 1 H); 7.40 (*d*, *J* = 8, 1 H); 7.64 (*d*, *J* = 7.5, 1 H); 8.05 (*d*, *J* = 10, 1 H). FAB-MS: small peak at 1282 (doubly allylated product), 1242.

[L-2-(Methylamino)pent-4-enoyl^3]CS (= *[L-MeNva(4,5-didehydro)^3]CS*; **3b**). According to *Method B*, 3.3 mmol of LDA in 7 ml of THF, a soln. of 635 mg (15 mmol) of LiCl and 0.83 g (0.5 mmol) of CS in 12 ml of THF, 3.3 mmol of BuLi, and 1.27 ml (15 mmol) of allyl bromide were used. The soln. was warmed to r.t. within 4 h and worked up as described for **2b**. LC (silica gel, Et_2O/MeOH 95:5) gave 58 mg of enriched (*ca.* 75%) **3a** and 445 mg of enriched (*ca.* 85–90%) **3b**. Total yield: 81%. ^{1}H-NMR ($CDCl_3$, 300 MHz): some characteristical signals of **3b**: 2.69 (2*s*, 6 H); 2.76 (*s*, 3 H); 3.12 (*s*, 3 H); 3.17 (*s*, 3 H); 3.20 (*s*, 3 H); 3.40 (*s*, 3 H); 7.17 (*d*, *J* = 8, 1 H); 7.69 (*d*, *J* = 7, 1 H); 7.88 (*d*, *J* = 9, 1 H); 8.17 (*d*, *J* = 8, 1 H). Anal. calc. for $C_{65}H_{115}N_{11}O_{12}$: C 62.85, H 9.27, N 12.41; found: C 62.46, H 9.47, N 11.71.

[D-2-(Methylamino)pent-4-ynoyl^3]CS (= *[D-MeNva(4,4,5,5-tetradehydro)^3]CS*; **4a**). According to *Method A*, 150 ml of THF, 1.6 ml (11.25 mmol) of (i-Pr)$_2$NH, 6.72 ml (10 mmol) of BuLi, 1.88 g (1.5 mmol) of CS in 50 ml of THF, and 1.785 g (15 mmol) of propargyl bromide (= 3-bromoprop-1-yne) were used. The temp. was allowed to rise to r.t. After 1 h stirring, 20 ml of H_2O were added slowly, and the solvent was evaporated to give 2.2 g of crude product. Purification by LC (220 g of silica gel, Et_2O/MeOH 96:4) gave 248 mg (13%) of pure **4a**. $[\alpha]_D^{20} = -214$ (*c* = 1.06, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.71 (*d*, *J* = 6, Me–C(4.1)); 0.80–1.20 (*m*, Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.28 (*d*, *J* = 6, Me–C(2.8)); 1.34 (*d*, *J* = 6, Me–C(2.7)); 1.48, 1.70, 2.10 (3*m*, H–C(4.1), H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6), 2 H–C(3.9), H–C(4.9), 2 H–C(3.10), H–C(4.10), H–C(3.11)); 1.63 (*d*, *J* = 3, Me–C(7.1)); 2.10 (*s*, H–C(5.3)); 2.40 (2*m*, H–C(5.1), H–C(3.5)); 2.68, 2.69 (2*s*, Me–N(2.10), Me–N(2.11)); 2.75 (*m*, 2 H–C(3.3)); 3.11 (*s*, Me–N); 3.21 (*s*, MeN); 3.28 (*s*, 2 MeN); 3.51 (*s*, MeN); 3.70 (*m*, H–C(3.1)); 4.53 (*m*, H–C(2.7)); 4.65 (*m*, H–C(2.5)); 4.83 (*m*, H–C(2.8)); 5.00, 5.10 (2*m*, H–C(2.2), H–C(2.3), H–C(2.6), H–C(2.10), H–C(2.11)); 5.34 (*m*, H–C(2.4), H–C(6.1), H–C(7.1)); 5.51 (*d*, *J* = 6, H–C(2.1)); 5.71 (*dd*, *J* = 12, 4, H–C(2.9)); 7.18 (*s*, H–N(2.8)); 7.37 (*s*, H–N(2.5)); 7.70 (*s*, H–N(2.7)); 8.18 (*s*, H–N(2.2)).

[ambo-MeAsp(O^{t}Bu)^3]CS (**5a**/**5b**). According to *Method A*, 600 ml of THF, 7 ml (49.2 mmol) of (i-Pr)$_2$NH, 29.7 ml (44.6 mmol) of BuLi, 8 g (6.6 mmol) of CS in 150 ml of THF, and 5 ml (33.2 mmol) of *tert*-butyl bromoacetate were used. After the addition of the electrophile, the temp. was risen to r.t. and the cloudy mixture stirred for 1 h. Then 100 ml of H_2O were added slowly and evaporated. The residue was dissolved in Et_2O/H_2O and the org. phase washed twice with H_2O, dried ($MgSO_4$), and evaporated: 12 g of oil. LC (440 g of silica gel, Et_2O/MeOH 96:4) provided 2.2 g of less polar fraction which was still not pure. A further LC of this fraction gave 1.68 g (19%) of pure [D-MeAsp(O^{t}Bu)^3]CS (**5a**). After chromatographic purification of the other polar fraction, 0.72 g (8%) of [MeAsp(O^{t}Bu)^3]CS (**5b**) were isolated. **5a**: $[\alpha]_D^{20} = -202$ (*c* = 1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.70 (*d*, *J* = 6, Me–C(4.1)); 0.75–1.15 (*m*, 39 H, 13 Me); 1.25 (*d*, *J* = 6, Me–C(2.8)); 1.34 (*d*, *J* = 6, Me–C(2.7)); 1.45 (*s*, *t*-Bu); 1.60 (*d*, *J* = 3, Me–C(7.1)); 1.40, 1.75, 2.10 (3*m*, 17 H as in CS); 2.38 (*m*, H–C(5.1), H–C(3.5)); 2.68, 2.69 (2*s*, Me–N(2.10), Me–N(2.11)); 2.79 (*d*, *J* = 6, 2 H–C(3.3)); 3.13 (*s*, Me–N(2.9)); 3.21, 3.22 (2*s*, Me–N(2.4), Me–N(2.6)); 3.28 (*s*, Me–N(2.3)); 3.47 (*m*, H–C(3.1)); 4.52 (*t*, *J* = 6, H–C(2.7)); 4.65 (*t*, *J* = 8, H–C(2.5)); 4.85 (*t*, *J* = 6, H–C(2.8)); 5.0, 5.7 (2*m*, H–C(2.2), H–C(2.6), H–C(2.10)); 5.10 (*d*, *J* = 12, H–C(2.11)); 5.25 (*t*, *J* = 6, H–C(2.3)); 5.30 (*dd*, *J* = 12, 4, H–C(2.4)); 5.34 (*m*, H–C(6.1), H–C(7.1)); 5.50 (*d*, *J* = 6, H–C(2.1)); 5.70 (*dd*, *J* = 12, 4, H–C(2.9)); 7.18 (*d*, *J* = 6, H–N(2.8)); 7.37 (*d*, *J* = 8, H–N(2.5)); 7.69 (*d*, *J* = 5, H–N(2.7)); 8.17 (*d*, *J* = 9, H–N(2.2)).

[D-MeAsp^3]CS. To 400 mg (0.30 mmol) of **5a**, 16 ml of CF_3COOH were added at ice-bath temp. After 2.5 h of stirring and evaporation, the residue was taken up in 50 ml of 2N NaOH and MeOH cautionally added (20–30 ml) until the soln. got clear. Then, at ice cooling, *ca.* 50 ml of 2N HCl were added to reach pH 1–2. The mixture was extracted 3 times with 150 ml of Et_2O and the org. layer washed with 100 ml of H_2O and 50 ml of sat. NaCl and 3 ml of sat. $NaHCO_3$ soln. The combined org. layer was dried ($MgSO_4$) and evaporated: 227 mg (59%) of [D-MeAsp^3]CS. ^{1}H-NMR ($CDCl_3$, 360 MHz): conformation similar to that of **5a**; 0.70 (*d*, *J* = 6, Me–C(4.1)); 0.80–1.20 (*m*, 39 H, 13 Me); 1.28 (*d*, *J* = 6, Me–C(2.8)); 1.38 (*d*, *J* = 6, Me–C(2.7)); 1.65 (*d*, *J* = 3, Me–C(7.1)); 1.40–2.50 (*m*, 19 H); 2.70 (*s*, Me–N(2.10), Me–N(2.11)); 2.90 (*m*, 2 H–C(3.3)); 3.15, 3.20, 3.25, 3.30, 3.50 (5*s*, 5 MeN); 3.71 (*m*, H–C(3.1)); 4.55 (*m*, H–C(2.7)); 4.65 (*m*, H–C(2.5)); 4.85 (*m*, H–C(2.8)); 5.00, 5.08 (2*m*, H–C(2.2), H–C(2.6), H–C(2.10)); 5.10 (*d*, *J* = 12, H–C(2.11)); 5.30 (*m*, H–C(2.3), H–C(2.4), H–C(6.1), H–C(7.1)); 5.50 (*d*, *J* = 6, H–C(2.1)); 5.70 (*dd*, *J* = 12, 4, H–C(2.9)); 7.20, 7.40, 7.68, 8.20 (4*d*, *J* = 8, 4 NH). FAB-MS: 1261 (MH^+), 1243 ($[MH - H_2O]^+$).

[D-MeAsp(OMe)^3]CS. To 200 mg of [D-MeAsp^3]CS, an excess of diazomethane in Et_2O was added. After 15 min, the solvent was evaporated and the crude product (220 mg) purified by LC (11 g of silica gel, Et_2O/MeOH 93:7): 125 mg (62%) of [D-MeAsp(OMe)^3]CS. $[\alpha]_D^{20} = -225$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.71 (*d*, $J = 6$, Me–C(4.1)); 0.80–1.20 (*m*, Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.27 (*d*, $J = 6$, Me–C(2.8)); 1.34 (*d*, $J = 6$, Me–C(2.7)); 1.40, 1.70, 2.10 (3*m*, H–C(4.1), H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6), 2 H–C(3.9), H–C(4.9), 2 H–C(3.10), H–C(4.10), H–C(3.11)); 1.62 (*d*, $J = 3$, Me–C(7.1)); 2.48 (2*m*, H–C(5.1), H–C(3.5)); 2.70 (*s*, Me–N(2.10), Me–N(2.11)); 2.35, 2.37 (2*d*, $J = 3$, 2 H–C(3.3)); 3.12, 3.18, 3.25, 3.27 (4*s*, Me–N(2.4), Me–N(2.9), Me–N(2.6), Me–N(2.3)); 3.43 (*d*, $J = 3$, OH–C(3.1)); 3.51 (*s*, Me–N(2.1)); 3.70 (sh, H–C(3.1)); 3.73 (*s*, MeOCO–C(3.3)); 4.53 (*t*, $J = 6$, H–C(2.7)); 4.64 (*t*, $J = 8$, H–C(2.5)); 4.83 (*t*, $J = 6$, H–C(2.8)); 5.00 (2*m*, H–C(2.6), H–C(2.10)); 5.10 (*m*, H–C(2.2)); 5.11 (*d*, $J = 12$, H–C(2.11)); 5.31 (*m*, H–C(2.4), H–C(6.1), H–C(7.1)); 5.50 (*d*, $J = 6$, H–C(2.1)); 5.71 (*dd*, $J = 12$, 4, H–C(2.9)); 7.19 (*d*, $J = 9$, H–N(2.8)); 7.36 (*d*, $J = 9$, H–N(2.5)); 7.70 (*d*, $J = 9$, H–N(2.7)); 8.18 (*d*, $J = 9$, H–N(2.2)).

[L-MeAsp(OMe)^3]CS. At 0°, 486 mg (10.37 mmol) of **5b** in 2 ml of CH_2Cl_2 were treated with 10 ml of CF_3COOH. After 2.5 h, the mixture was poured into a cold soln. of 15 g $KHCO_3$ in 50 ml of H_2O and extracted twice with CH_2Cl_2. The dried ($MgSO_4$) org. layers were evaporated. To the crude product in 25 ml of Et_2O, excess diazomethane in Et_2O was added. After 2 h, the solvent was evaporated and the residue chromatographed (60 g of silica gel, Et_2O/MeOH 93:7): 215 mg (46%) of [L-MeAsp(OMe)^3]CS. $[\alpha]_D^{20} = -211$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): more than 3 conformations. ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.77 (*d*, $J = 6$, Me–C(4.1)); 0.80–1.00 (*m*, 39 H, 13 Me); 1.20, 1.21 (2*d*, $J = 6$, Me–C(2.7), Me–C(2.8)); 1.50, 1.80, 2.10, 2.30 (4*m*, 19 H as for CS); 2.50 (*dd*, $J = 14$, 4, 2 H–C(3.3)); 2.87, 2.88 (2*s*, 2 MeN); 2.92, 2.93 (2*s*, 2 MeN); 3.00 (*s*, MeN); 3.20 (*s*, MeN); 3.50 (*s*, MeN); 3.60 (*s*, MeOCO–C(3.3)); 3.98 (*m*, H–C(3.1)); 4.38 (*m*, H–C(2.7)); 4.58 (*m*, H–C(2.5)); 4.76, 4.80 (2*m*, H–C(2.1), H–C(2.6), H–C(2.8), H–C(2.10)); 4.95 (*t*, H–C(2.2)); 5.10 (*d*, $J = 12$, H–C(2.11)); 5.45 (*m*, H–C(2.4), H–C(2.9), H–C(6.1), H–C(7.1)); 5.75 (*m*, H–C(2.3)); 6.9–7.4 (br. *s*, 4 NH). FAB-MS: 1274 (MH^+).

[D-MePhe^3]CS (**6a**). A cooled (−75°) THF soln. (50 ml) of 1 g (0.83 mmol) of CS was treated with 15 equiv. of LDA soln. The resulting clear light yellow soln. was stirred for 1 h at −75°. Then 3.0 ml (25.3 mmol) of benzyl bromide were added. The mixture was stirred at −75° for 6 h and warmed to r.t. for additional 10 h followed by quenching with 10 ml of H_2O. After evaporation of the THF, the aq. residue was extracted with Et_2O, the Et_2O phase dried ($MgSO_4$) and evaporated, and the residue chromatographed (silica gel, Et_2O/MeOH 95:5): 242 mg (23%) of **6a** (contaminated with some doubly benzylated product). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.7–1.05 (*m*, 47 H); 1.24 (*d*, $J = 7$, 2 H); 1.32 (*d*, $J = 7$, 3 H); 1.5–2.2 (*m*, 13 H); 2.43 (*s*, 3 H); 2.68 (*s*, 3 H); 2.70 (*s*, 3 H); 3.10 (*s*, 3 H); 3.24 (*s*, 3 H); 3.35 (*s*, 3 H); 3.52 (*s*, 3 H); 3.65 (*m*, 1 H); 3.74 (br. *s*, 1 H); 4.52 (*m*, 2 H); 4.80–5.35 (*m*, 11 H); 5.54 (*d*, $J = 6$, 1 H); 5.72 (*d*, $J = 11$, 1 H); 7.13 (*d*, $J = 8$, 1 H); 7.17–7.34 (*m*, 5 H); 7.36 (*d*, $J = 4.5$, 1 H); 7.61 (*d*, $J = 8$, 1 H); 8.14 (*d*, $J = 10$, 1 H). FAB-MS: small signal at 1382 (doubly benzylated product), 1292.

[D-MeSer^3]CS (**7a**). According to *Method A*, 60 ml of THF, 0.87 ml (6.16 mmol) of (i-Pr)$_2$NH, 3.9 ml (5.46 mmol) of BuLi, and 1 g (0.83 mmol) of CS in 15 ml of THF were used. Separately, 2 g of paraformaldehyde[17]) were heated to 170° and transferred as monomeric formaldehyde to the enolate soln. *via* a *Teflon* tube. During the transfer (1 h), the first flask had to be cooled to −94° to obtain −70° in the reaction mixture, then 20 ml of H_2O were added slowly, followed by 200 ml of Et_2O. The org. phase was washed 5 times with 200 ml of H_2O, dried ($MgSO_4$), and evaporated and the residue purified by LC (100 g of silica gel, AcOEt sat. with H_2O) to give 430 mg (42%) of **7a**. $[\alpha]_D^{20} = -217$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.70 (*d*, $J = 6$, Me–C(4.1)); 0.80–1.15 (*m*, Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.25 (*d*, $J = 6$, Me–C(2.8)); 1.30 (*d*, $J = 6$, Me–C(2.7)); 1.45, 1.70, 2.10 (3*m*, H–C(4.1), H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6), 2 H–C(3.9), H–C(4.9), 2 H–C(3.10), H–C(4.10), H–C(3.11)); 1.60 (*d*, $J = 3$, Me–C(7.1)); 2.40 (*m*, H–C(5.1), H–C(3.5)); 2.68, 2.69 (2*s*, Me–N(2.10), Me–N(2.11)); 3.15, 3.18 (2*s*, Me–N(2.4), Me–N(2.9)); 3.27, 3.32 (2*s*, Me–N(2.6), Me–N(2.3)); 3.50 (*s*, Me–N(2.1)); 3.18, 3.25 (2*m*, H–C(3.1), OH–C(3.1)); 4.03 (*d*, $J = 6$, 2 H–C(3.3); double resonance at 4.03→*s* at 5.00 (H–C(2.3)); 4.53 (*t*, $J = 6$, H–C(2.7)); 4.66 (*t*, $J = 8$, H–C(2.5)); 4.83 (*t*, $J = 6$, H–C(2.8)); 5.00, 5.09 (2*m*, H–C(2.2), H–C(2.3), H–C(2.6), H–C(2.10)); 5.13 (*d*, $J = 12$, H–C(2.11)); 5.32 (*m*, H–C(2.4), H–C(6.1), H–C(7.1)); 5.50 (*d*, $J = 5$, H–C(2.1)); 5.71 (*dd*, $J = 12$, 4, H–C(2.9)); 7.18 (*d*, $J = 6$, H–N(2.8)); 7.50 (*d*, $J = 6$, H–N(2.5)); 7.68 (*d*, $J = 6$, H–N(2.7)); 8.10 (*d*, $J = 8$, H–N(2.2)).

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[17]) A well stirred soln. of 1 l of 35% formalin was treated with 7.4 g of solid NaOH and stirred for a week. After standing for 3 d, the precipitated paraformaldehyde was separated over a *Büchner* funnel, washed with 500 ml of cold H_2O, and dried in the air (2–3 d) and finally (as a fine powder) over P_2O_5 in a desiccator (2 d).

[D-MeSer(OBz)^3]CS (**8a**). A pyridine soln. (25 ml) of 1.12 g of **7a** was cooled to 0° and treated with 10 ml of benzoyl chloride. After stirring for 1.5 h at 0°, the soln. was diluted with Et_2O and washed 3 times with 3N HCl. The org. phase was dried ($MgSO_4$), evaporated, and chromatographed (silica gel, Et_2O/MeOH 97:3): 0.922 g (41%) of **8a**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.72–1.45 (*m*, 47 H); 1.5–2.5 (*m*, 13 H); 2.69 (*s*, 3 H); 2.70 (*s*, 3 H), 3.12 (*s*, 3 H); 3.16 (*s*, 3 H); 3.25 (*s*, 3 H); 3.40 (*s*, 3 H); 3.51 (*s*, 3 H); 3.78 (br. *s*, 2 H); 4.50–5.48 (*m*, 14 H); 5.71 (br. *s*, 1 H); 7.17–7.66 (*m*, 5 H); 7.98–8.11 (*m*, 4 H). FAB-MS: 1336.

[D-MeSer(OCOCHN$_2$)^3]CS (**9a**). Under Ar, **7a** (30 mg) was dissolved in 0.5 ml of CH_2Cl_2 at r.t. After cooling in an ice-bath, 6.5 mg of glyoxyoyl chloride 4-toluenesulfonylhydrazone [27] and 10 µl of Et_3N were added. The resulting clear yellow soln. was stirred for 1 h at 0° and then hydrolyzed with 10 ml of H_2O, the mixture extracted 3 times with Et_2O, and the org. layer dried ($MgSO_4$) and evaporated: 27 mg of **7a**/**9a**. Anal. HPLC (*Lichrosorb RP 18* (10 µm), 250 × 4 mm; $MeCNH_2O$ 65:4): 12% of **7a** in mixture.

[D-MeSer(3-oxo)^3]CS (**10a**). According to *Method A*, 5.6 mmol of LDA, 50 ml of THF, and 0.83 mmol of CS in 15 ml of THF were used. After stirring for 1 h at −78°, a stream of CO_2-gas was passed through the mixture for 15 min. After 1 h stirring the soln. was poured in 2N H_3PO_4 and extracted with Et_2O. The org. layer was dried ($MgSO_4$) and evaporated to yield 1.10 g of crude **10a**/CS. At 4°, **10a** is stable in the solid state for weeks; in soln., decarboxylation takes place within h. ^{1}H-NMR ($CDCl_3$, 360 MHz): 55% of **10a** and 45% of CS; 5.90 (*s*, H–C(2.3)).

[D-MeSer(OMe,3-oxo)^3]CS (**11a**). According to *Method A*, 1200 ml of THF, 17 ml (120 mmol) of $(i\text{-Pr})_2NH$), 80 ml (112.5 mmol) of BuLi, and 18 g (15.0 mmol) of CS in 300 ml of THF were used. After stirring for 1 h at −78°, a stream of CO_2 gas was passed through until the mixture became clear (*ca.* 40 min). After CO_2 was passed through for additional 5 min, 11.5 ml (150 mmol) of methyl chloroformate were slowly added (without pretreatment with CO_2, no reaction with ClCOOMe was observed) and stirred for 2 h at −78°. Then 1.7 ml (12 mmol) of $(i\text{-Pr})_2$ NH were added. The mixture was warmed to r.t., stirred overnight, and then refluxed for 30 min (→clear soln.). The cooled mixture was poured upon dil. H_3PO_4 soln. (pH 3), extracted 3 times with Et_2O, and the combined org. layer washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated: 40 g of crude product. LC (2.2 kg of silica gel, Et_2O/MeOH 97:3) provided 7.6 g (40%) of **11a** (containing *ca.* 5% of the L-diastereoisomer **11b**, according to NMR). $[\alpha]_D^{20} = -197$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.71 (*d*, *J* = 6, Me–C(4.1)); 0.80–1.15 (*m*, 13 Me–C, as for CS); 1.25 (*d*, *J* = 6, Me–C(2.8)); 1.34 (*d*, *J* = 8, Me–C(2.7)); 1.48, 1.71, 2.10 (3*m*, 17 H, as in CS); 1.60 (*d*, *J* = 3, Me–C(7.1)); 2.38 (*m*, H–C(5.1), H–C(3.5)); 2.18, 2.19 (2*s*, Me–N(2.10), Me–N(2.11)); 3.10 (*s*, Me–N(2.4)); 3.6 (*s*, Me–N(2.9)); 3.28 (*s*, Me–N(2.6)); 3.35 (*s*, Me–N(2.3)); 3.50 (*s*, Me–N(2.1)); 3.78 (*m*, H–C(3.1)); 3.85 (*s*, MeOCO–C(2.3)); 4.52 (*t*, *J* = 8, H–C(2.7)); 4.65 (*t*, *J* = 8, H–C(2.5)); 4.85 (*t*, *J* = 6, H–C(2.8)); 4.95–5.10 (*m*, H–C(2.2), H–C(2.6), H–C(2.10)); 5.12 (*d*, *J* = 12, H–C(2.11)); 5.35 (*m*, H–C(2.4), H–C(6.1), H–C(7.1)); 5.50 (*d*, *J* = 3, H–C(2.1)); 5.70 (*dd*, *J* = 12, 4, H–C(2.9)); 5.90 (*s*, H–C(2.3)); 7.08 (*d*, *J* = 6, H–N(2.8)); 7.20 (*d*, *J* = 6, H–N(2.5)); 7.75 (*d*, *J* = 6, H–N(2.7)); 8.08 (*d*, *J* = 8, H–C(2.2)).

[ambo-Sar(2-SMe)^3]CS (**12a**/**12b**). Without LiCl: According to *Method B*, with 0.601 g (0.5 mmol) of CS in 15 ml of THF, 15 equiv. of LDA soln., 6 equiv. of BuLi, and 0.9 ml (10 mmol) of Me_2S_2. The temp. was allowed to rise to 0°. After 17 h, 20 ml of 1N HCl were added and the mixture worked up with Et_2O, the org. phase washed 2 times with sat. $NaHCO_3$ soln. and 2 times with sat. NaCl soln., dried ($MgSO_4$), and evaporated: 0.56 g of crude **12a**/**12b**. ^{1}H-NMR ($CDCl_3$, 300 MHz): **12a**/**12b**: 76.5:23.5; 5.77 (*s*, H–C(2.3) of **12a**); 6.28, 6.93 (2*s*, H–C(2.3) of **12b**).

With LiCl: According to *Method B*, with 0.601 g (0.5 mmol) of CS and 0.636 g (15 mmol) of LiCl in 20 ml of THF, 6.5 equiv. of LDA soln., 6.0 equiv. of BuLi, and 0.9 ml (10 mmol) of Me_2S_2. Workup after 18 h at 0° stirring as described for reaction without LiCl. Separation after two LC (silica gel, AcOEt sat. with H_2O) gave 84 mg (14%) of CS, 50 mg (8%) of **12a**, and 340 mg (54%) of **12b**.

[D-Sar(2-SMe)^3]CS (**12a**). M.p. 140–143°. $[\alpha]_D^{20} = -213$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.71 (*d*, *J* = 6, aliph. H); 0.76–1.14, 1.18–1.54, 1.54–1.84, 1.88–2.18 (4*m*, aliph. H); 2.14 (*s*, MeS); 2.34–2.52 (*m*); 2.69, 2.70, 3.00, 3.11, 3.26, 3.43, 3.50 (7*s*, MeN); 3.63–3.73, 3.74–3.84 (2*m*); 4.55 (*m*, H–C(2.7)); 4.67 (*m*, H–C(2.5)); 4.85 (*m*, H–C(2.8)); 4.97 (*m*, H–C(2.4), H–C(2.6) or H–C(2.10)); 5.04–5.13 (*m*, H–C(2.2)); 5.14 (*d*, *J* = 12, H–C(2.11)); 5.26 (*dd*, *J* = 12, 4, H–C(2.4), H–C(2.6) or H–C(2.10)); 5.31–5.39 (*m*, 2 H); 5.50 (*d*, *J* = 5, H–C(2.1)); 5.71 (*dd*, *J* = 12, 4, H–C(2.9)); 5.79 (*s*, H–C(2.3)); 7.17, 7.35, 7.66 (3*d*, *J* = 8, NH); 7.94 (*d*, *J* = 10, NH).

[L-Sar(2-SMe)^3]CS (**12b**). M.p. 157–159°. $[\alpha]_D^{20} = -185$ (*c* = 1.25, $CHCl_3$). ^{1}H-NMR (3 conformations in $CDCl_3$, 300 MHz): 0.64–1.12, 1.15–2.50 (2*m*, aliph. H); 2.08 (*s*, MeS); 2.70, 2.71, 2.77, 2.78, 2.79, 2.80, 2.87, 2.89, 2.91, 2.95, 2.96, 2.98, 3.02, 3.10, 3.13, 3.17, 3.19, 3.20, 3.25, 3.38, 3.40 (21 H, 7 MeN); 3.44–3.96, 3.98–4.18, 4.22–4.31 (3*m*, 1 H); 4.44–4.56 (*m*, 1 H), 4.62–5.74 (*m*, 11 H); 6.30 (*s*); 6.45 (*s*); 6.54–6.64, 6.64–6.80 (2*m*); 6.94 (*s*); 7.14–7.24 (*m*, NH); 7.48 (*d*, *J* = 8, NH); 7.80 (*d*, *J* = 6, NH); 7.99 (*d*, *J* = 8, NH); 7.64, 7.85, 8.25, 8.65, 8.84 (5*d*, NH signals of conformers).

*[*ambo-*Sar(2-(4-MeC$_6$H$_4$S))^3]CS* (**13a**/**13b**). According to *Method B*, 0.601 g (0.5 mmol) of CS and 0.70 g (16.5 mmol) of LiCl in 20 ml of THF, 3.3 mmol of LDA soln., 3.0 mmol of BuLi, and di(tol-4-yl) disulfide. Workup after 18 h at 0° stirring as described for **12a**/**12b**. Separation after three LC (silica gel, AcOEt sat. with H_2O) provided 28 mg (5%) of CS, 226 mg (34%) of **13a**, and 313 mg (47%) of **13b**.

*[*D-*Sar(2-(4-MeC$_6$H$_4$S))^3]CS* (**13a**). M.p. 144–146°. $[\alpha]_D^{20} = -214.8$ ($c = 1.33$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.72 (*d*, $J = 6$, Me–C(4.1)); 0.78–1.12, 1.17–1.54, 1.56–1.84, 1.93–2.21 (4*m*, aliph. H); 2.34 (*s*, *Me*C$_6$H$_4$); 2.38–2.50 (*m*); 2.69, 3.08, 3.12, 3.25, 3.51 (5*s*, 7 MeN); 3.72–3.82 (*m*, 1 H); 4.54 (*m*, H–C(2.7)); 4.66 (*m*, H–C(2.5)); 4.85 (*m*, H–C(2.8)); 4.94–5.13 (*m*, 3.5 H, H–C(α)); 5.26 (*dd*, $J = 6$, 12, H–C(α)); 5.31–5.39 (*m*, 1.5 H, H–C(α)); 5.50 (*d*, $J = 6$, H–C(2.1)); 5.72 (*dd*, $J = 6$, 10, H–C(2.9)); 6.12 (*s*, H–C(2.3)); 7.12–7.28 (*m*, 2 NH, MeC$_6$*H*$_4$); 7.69 (*d*, $J = 8$, NH); 8.01 (*d*, $J = 8$, NH). ^{13}C-NMR ($CDCl_3$): 9.79, 15.90, 16.86, 17.89, 18.11, 18.39, 18.68, 19.82, 20.27, 21.10, 21.82, 23.39, 23.49, 23.69, 23.80, 24.43, 24.63, 24.82, 25.04, 25.30, 29.10, 29.57, 29.79, 30.61, 31.13, 31.51, 32.88, 33.85, 35.52, 35.92, 37.41, 39.00, 40.58, 45.05, 48.18, 48.49, 50.42, 55.22, 55.30, 55.43, 57.51, 57.93, 58.94, 63.90, 74.74, 126.30, 129.31, 129.57, 130.41, 130.53, 138.59, 169.85, 170.11, 170.39, 171.14, 171.61, 173.56, 174,96. FAB-MS: 1328 (4.7), 1327 (9.6), 1326 (34.3), 1325 (70.4), 1324 (90.0), 1323 (114.4), 1322 (21.0), 1307 (4.8), 932 (5.7), 692 (3.2), 239 (5.3), 225 (5.8), 224 (17.5), 211 (3.4), 210 (7.7), 197 (11.6), 169 (11.8), 168 (5.6), 166 (5.4), 156 (6.0), 155 (6.0), 154 (8.1), 141 (5.9), 140 (7.6), 126 (7.5), 113 (8.2), 112 (5.5), 101 (6.3), 100 (100), 99 (4.0), 98 (13.0), 89 (6.9), 86 (10.6), 84 (10.2), 77 (9.9), 68 (7.3), 63 (6.9), 58 (12.5), 57 (12.4), 56 (8.6), 55 (24.3), 53 (9.9), 51 (14.1), 50 (11.5), 44 (17.9), 43 (260), 42 (31.1), 41 (51.1), 39 (71.1).

*[*L-*Sar(2-(4-MeC$_6$H$_4$S))^3]CS* (**13b**). M.p. 145–151°. $[\alpha]_D^{20} = -221.1$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (more than one conformation in $CDCl_3$, 300 MHz): 0.70 (*d*, $J = 6$, Me–C(4.1)); 0.76–1.06 (*m*, aliph. H); 1.09 (*d*, $J = 6$, aliph. H); 1.16–1.40, 1.51–1.71, 1.71–1.96, 2.00–2.30 (4*m*, aliph. H); 2.30 (*s*, *Me*C$_6$H$_4$); 2.69, 2.70 (2*s*, 2 MeN); 2.78–3.07 (*m*); 2.82, 3.12, 3.20, 3.41, 3.45 (5*s*, 2 MeN); 3.60–3.72, 4.03–4.14 (2*m*, 2 H); 4.42–4.56 (*m*, H–C(α)); 4.56–4.68 (*m*, H–C(α)); 4.80–5.00 (*m*, H–C(α)); 5.04 (*d*, $J = 12$, H–C(2.11)); 5.11–5.60 (*m*, 6 H–C(α)); 5.69 (*dd*, H–C(2.9)); 6.75 (*s*, H–C(2.3)); 7.01–7.36 (*m*, 2 NH, MeC$_6$*H*$_4$); 7.69–7.75 (*m*, NH); 8.00 (*d*, $J = 8$, NH); 8.15, 8.63, 8.82 (3*d*, NH signals of conformers). ^{13}C-NMR ($CDCl_3$): 10.42, 10.68, 15.79, 16.00, 16.65, 16.79, 17.85, 18.00, 18.23, 18.49, 18.71, 18.99, 19.13, 19.44, 19.72, 19.91, 20.07, 20.46, 21.04, 21.40, 21.62, 21.69, 21.82, 22.02, 22.25, 22.42, 22.72, 22.85, 23.01, 23.15, 23.31, 23.46, 23.70, 23.82, 24.01, 24.24, 24.34, 24.64, 24.80, 24.96, 25.12, 25.21, 25.51, 25.86, 28.85, 29.07, 29.24, 29.62, 29.81, 30.04, 30.26, 30.34, 30.44, 30.54, 30.65, 30.82, 30.94, 31.37, 31.69, 33.44, 33.57, 33.84, 33.93, 35.64, 36.38, 37.07, 37.52, 38.02, 38.17, 38.32, 39.17, 40.76, 44.91, 45.42, 48.17, 48.52, 49.75, 50.47, 51.31, 51.82, 52.74, 53.64, 54.25, 54.51, 54.75, 55.73, 57.40, 58.49, 58.66, 58.96, 61.70, 62.08, 64.09, 71.73, 72.19, 77.27, 126.18, 126.86, 126.98, 127.32, 127.78, 128.86, 129.84, 130.13, 130.43, 130.58, 133.15, 135.44, 137.48, 167.46, 167.75, 168.37, 168.49, 169.01, 169.13, 170.30, 170.38, 170.50, 170.69, 171.07, 171.24, 171.38, 171.53, 171.99, 172.19, 172.35, 172.57, 172.70, 173.44, 173.71. FAB-MS: 1325 (39.6), 1324 (24.2), 1322 (4.1), 1201 (4.1), 933 (6.7), 819 (4.3), 692 (4.9), 423 (9.5), 296 (7.7), 270 (6.3), 253 (7.0), 239 (6.7), 225 (13.6), 224 (30.6), 212 (5.7), 211 (9.4), 210 (16.3), 209 (6.5), 199 (9.9), 198 (17.6), 197 (41.5), 184 (8.2), 183 (16.5), 182 (20.4), 169 (30.8), 168 (24.0), 167 (9.6), 166 (25.6), 156 (29.1), 155 (19.7), 154 (41.6), 141 (19.5), 140 (25.1), 138 (11.9), 137 (14.3), 136 (14.6), 128 (19.5), 127 (13.6), 126 (20.9), 125 (9.7), 124 (10.6), 114 (9.3), 113 (16.5), 112 (17.6), 101 (28.5), 100 (100), 99 (14.1), 98 (48.3), 97 (19.2), 96 (11.2), 91 (9.5), 86 (49.7), 84 (40.1), 83 (18.3), 82 (14.5), 77 (11.1), 72 (23.4), 71 (11.9), 70 (19.4), 69 (24.4), 68 (9.7), 58 (57.7), 57 (30.7), 56 (20.5), 55 (56.4), 44 (55.6), 43 (31.7), 42 (65.9), 41 (36.3), 39 (22.6).

Further Cyclosporines with a Side Chain at Amino-Acid Residue 3. See *Table 1*.

Table 1. *Some Physical Data of Cyclosporines with a Side Chain at Amino-Acid Residue 3.* Except for the first one, all compounds listed here belong to the **a** series (see *Scheme 2*).

L-PhCH(OH)	Physical data	m.p. 162–167°
$AcOCH_2$		TLC (silica gel, CH_2Cl_2/MeOH 9:1): R_f 0.5
PhS		$[\alpha]_D^{r.t.} = -220$ ($c = 0.965$, $CHCl_3$)
CH_2=C(Cl)CH_2		−199 ($c = 0.5$, $CHCl_3$)
MeNHCO		−174 ($c = 0.9$, $CHCl_3$)
$HO(CH_2)_2S$		−187 ($c = 0.6$, $CHCl_3$)
$Ac(CH_2)_2S$		−186 ($c = 1.34$, $CHCl_3$)
Et		−204 ($c = 0.5$, $CHCl_3$)
CH_2=C(Me)CH_2		−201 ($c = 0.5$, $CHCl_3$)
PhCH=$CHCH_2$		−247 ($c = 0.5$, $CHCl_3$)
(Pyrid-2-yl)S		−244 ($c = 0.5$, $CHCl_3$)
(*E*)-CH(Cl)=$CHCH_2$		−218 ($c = 0.5$, $CHCl_3$)
CCl_2=$CHCH_2$		−222 ($c = 0.5$, $CHCl_3$)
(*Z*)-CH(Cl)=$CHCH_2$		−236 ($c = 0.5$, $CHCl_3$)

4. *N^5-Methylation of CS: [MeVal^5]CS* (**14**) [28]. A soln. of 600 mg (0.5 mmol) of CS in 20 ml of THF was treated at −78° with 0.63 ml (1.0 mmol) of BuLi. The resulting soln. was reacted with 0.1 ml (1.5 mmol) of dimethyl sulfate. The mixture was slowly warmed to r.t., stirred overnight, and worked up as usual. Although *ca.* 60% conversion was observed from the NMR of the crude product, only a small amount of the desired **14** was obtained in pure form after LC (silica gel, Et_2O/MeOH 95:5) and prep. reversed-phase HPLC (MeOH/H_2O 83:17). ^{1}H-NMR (more than one conformation in $CDCl_3$, 300 MHz; only MeN and NH); 2.75 (*s*, 3H); 2.83 (*s*, 3H); 2.87 (*s*, 3H); 2.91 (*s*, 3H); 2.96 (*s*, 3H); 2.98 (*s*, 3H); 3.07 (*s*, 3H); 6.0 (*d*, *J* = 8, NH); 6.40 (*d*, *J* = 8, NH); 6.82 (*d*, *J* = 8, NH).

5. *Ring Opening of CS: H-MeLeu-MeVal-MeBmt-Abu-Sar-MeLeu-Val-MeLeu-Ala-*D*-Ala-MeLeu-Bu* (**15**). A soln. of 1.202 g (1.0 mmol) of CS and 0.763 g (18.0 mmol) of LiCl in 30 ml of THF was treated at −75° with 9.76 ml (14.0 mmol) of BuLi. After 16 h of stirring at −75°, 10 ml of 6N HCl were added and warmed up. The mixture was taken up in 350 ml of Et_2O and the soln. washed twice with 250 ml of sat. $NaHCO_3$ and 250 ml of sat. NaCl soln., dried ($MgSO_4$), and evaporated: 2.56 g of crude product. Purification by LC (silica gel, Et_2O/MeOH 9:1) provided 430 mg (34%) of **15** and 364 mg (30%) of CS. **15**: M.p. 108–110°. $[\alpha]_D^{20} = -187.7$ (*c* = 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.54–0.66, 0.67–1.16, 1.18–1.47, 1.47–1.71, 1.71–1.96 (5*m*, aliph. H); 2.20–2.59 (*m*); 2.27 (*s*, Me–N(2.1)); 2.84, 2.91, 2.96, 3.08, 3.32, 3.35 (6*s*, 6H, 6MeN); 2.90, 2.98, 3.05, 3.14, 3.29, 3.44 (6*s*, 12H, 6MeN); 3.50–3.91 (*m*); 4.25–4.52, 4.77–4.92, 4.94–5.10, 5.10–5.29, 5.29–5.54 (5*m*, 12H–C(α)); 7.02 (*d*, *J* = 9, 0.7H, NH); 7.04 (*d*, *J* = 8, 0.7H, NH); 7.13 (*d*, *J* = 7, 0.3H, NH); 7.46–7.54 (*m*, NH); 7.61 (*d*, *J* = 6, 0.3H, NH); 7.66 (*d*, *J* = 9, 0.7H, NH); 8.25 (*d*, *J* = 6, 0.3H, NH). ^{1}H-NMR (300 MHz, (D_6)DMSO, 180°): 0.77–0.94, 0.94–1.10 (2*m*, aliph. H); 1.21, 1.22 (2*d*, *J* = 7, H–C(3.9) or H–C(3.10)); 1.24–1.35, 1.48–1.64, 1.67–1.99, 1.98–2.12, 2.22–2.42, 2.42–2.70 (6*m*, aliph. H); 2.84, 2.88, 2.89, 2.94, 2.97, 2.99 (6*s*, MeN); 2.09 (*s*); 3.94 (*dd*, *J* = 6.6, H–C(3.3)); 4.10–4.19, 4.26–4.37, 4.66–4.73 (3*m*, 5H–C(α)); 4.62 (*dd*, *J* = 6.8, H–C(2.7)); 4.74–4.85 (*m*, 3H–C(α)); 4.96 (*t*, *J* = 9, H–C(α)); 5.02 (*d*, *J* = 6, H–C(2.3)); 5.21 (*d*, *J* = 9, H–C(2.2)); 5.37–5.43 (*m*, H–C(6.3), H–C(7.3)); 6.84–7.06 (*m*, 2.8H, NH); 7.25–7.36 (*m*, 1.2H, NH). ^{13}C-NMR ($CDCl_3$): 9.59, 9.97, 13.89, 15.38, 15.51, 15.70, 16.90, 17.71, 17.96, 18.17, 18.35, 18.54, 18.62, 19.20, 19.39, 19.64, 19.75, 19.84, 20.00, 21.11, 21.22, 21.33, 21.49, 21.67, 21.81, 21.98, 22.14, 22.30, 22.71, 23.05, 23.22, 23.44, 23.69, 24.58, 24.70, 24.92, 25.05, 25.20, 25.31, 25.63, 25.80, 26.77, 26.90, 27.00, 29.13, 29.67, 29.82, 30.07, 30.40, 30.50, 30.81, 30.97, 31.10, 31.53, 34.38, 34.70, 35.06, 35.19, 35.44, 35.77, 35.95, 36.36, 36.50, 36.71, 37.07, 37.45, 37.69, 37.94, 38.33, 38.49, 38.78, 39.56, 42.86, 45.82, 45.94, 48.81, 49.24, 49.39, 49.52, 49.70, 49.86, 50.16, 53.94, 54.67, 54.97, 55.29, 55.51, 56.14, 57.35, 57.67, 57.84, 58.00, 58.12, 58.32, 58.43, 58.79, 60.41, 75.05, 75.88, 76.36, 77.27, 126.64, 127.25, 128.64, 129.33, 168.76, 170.00, 170.24, 170.34, 170.43, 170.83, 170.98, 171.33, 171.41, 171.52, 171.89, 171.99, 172.24, 172.42, 173.03, 173.18, 173.27, 175.86, 175.96, 208.44, 208.63. FAB-MS (Xaa = amino-acid residue): 1261 (100, M^+), 1076 (4.6, [M − Xaa^{11}]$^+$), 1021 (4.1, [M − Xaa^1 − Xaa^2]$^+$), 934 (3.7, [M − Xaa^{11} − Xaa^{10} − Xaa^9]$^+$), 838 (4.1, [M − Xaa^1 to Xaa^3]$^+$), 753 (12, [M − Xaa^1 to Xaa^4]$^+$), 580 (7.1, [M − Xaa^{11} to Xaa^6]$^+$), 510 (3.3, [M − Xaa^{11} to Xaa^5]$^+$), 455 (7.1, [M − Xaa^1 to Xaa^7]$^+$), 425 (20, [M − Xaa^{11} to Xaa^4]$^+$), 354 (9.1), 328 (12, [M − Xaa^1 to Xaa^8]$^+$), 312 (34), 298 (22), 279 (12), 269 (12), 257 (9.5, [M − Xaa^1 to Xaa^9]$^+$), 241 (53, [M − Xaa^{11} to Xaa^3]$^+$), 239 (26), 214 (49), 199 (57), 187 (18).

6. *Synthesis of [*D*-MeAla^3]CS* (**2a**). N-(tert-*Butyloxycarbonyl*)-L-*2-aminobutyryl*-N-*methyl*-D-*alanine Benzyl Ester* (*Boc-Abu-*D*-MeAla-OBzl*; **18**). To a soln. of 15 g (74 mmol) of Boc-Abu-OH (**16**) in 200 ml of $CHCl_3$ precooled to −20°, 10 ml (9.8 g, 81 mmol) of pivaloyl chloride and 15 g (16.3 ml, 148 mmol) of MeMorph were added. The mixture was stirred for 4 h at −20° under N_2. A soln. of 17.1 g (88 mmol, 1.2 equiv.) of H-D-MeAla-OBzl (**17**; freshly prepared from H-D-MeAla-OBz·TsOH by shaking in $CHCl_3$ with sat. $NaHCO_3$ soln., drying (Na_2SO_4), and evaporation) in 100 ml of $CHCl_3$ was added and the mixture stirred for 3 d at −20° under N_2. Then the soln. was warmed to r.t. and washed with 200 ml of 1N HCl, the aq. phase extracted with 200 ml of CH_2Cl_2, and the combined org. phase dried (K_2CO_3), filtered, and evaporated. The residue (31 g) was chromatographed (360 g of silica gel, 1.5% MeOH/CH_2Cl_2): 23.8 g (85%) of **18**. $[\alpha]_D^{20} = +35.9$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 180°): 0.87 (*t*, *J* = 6, Me–C(3.1)); 1.40 (*d*, *J* = 6, Me–C(2.2)); 1.41 (*s*, *t*-Bu); 1.55, 1.70 (2*m*, 2H–C(3.1)); 2.95 (*s*, Me–N(2.2)); 4.40 (*m*, H–C(2.1)); 4.90 (*m*, H–C(2.2)); 5.18 (*s*, PhCH_2); 5.89 (br. *s*, H–N(2.1)); 7.35 (*s*, *Ph*CH_2). FD-MS: 378 (M^+), 379 (MH$^+$). Anal. calc. for $C_{20}H_{30}N_2O_5$ (378.473): C 63.5, H 8.0, N 7.4, O 21.8; found: C 62.8, H 7.8, N 7.5, O 21.5.

N-(tert-*Butyloxycarbonyl*)-L-*2-aminobutyryl*-N-*methyl*-D-*alanine* (*Boc-Abu-*D*-MeAla-OH*; **19**). A soln. of 22.8 g (60.3 mmol) of **18** in 500 ml of abs. EtOH was hydrogenated for 1 h using 2 g of 10% Pd/C and 1.4 l of H_2. The suspension was filtered through talc, the filtrate evaporated, the residue dissolved in CH_2Cl_2 (300 ml), and the soln. dried (Na_2SO_4), filtered, and evaporated. The residue was dried under high vacuum: 17.7 g (quant.) of **19**. White foam. $[\alpha]_D^{20} = -60$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 180°): 0.98 (*m*, Me–C(3.1)); 1.31 (*d*,

J = 8, Me–C(2.2)); 1.40 (s, *t*-Bu); 1.55, 1.70 (2*m*, 2H–C(3.1)); 2.92 (*s*, Me–N(2.2)); 4.35 (*m*, H–C(2.1)); 4.77 (*m*, H–C(2.2)); 5.70 (br. *s*, H–N(2.1)); 6.5–7.5 (COOH). FD-MS: 289 (MH$^+$). Anal. calc. for $C_{13}H_{24}N_2O_5$ (288.346): C 54.2, H 8.4, N 9.7, O 27.7; found: C 53.5, H 8.6, N 9.5, O 28.2.

N-*(* tert-*Butyloxycarbonyl)*-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **21**). As described for **18**, with 17.7 g (60.3 mmol) of **19**, 400 ml of $CHCl_3$, 8 g (8.15 ml, 66 mmol) of pivaloyl chloride, 14 ml (12.8 g, 126 mmol) of MeMorph, 32 g (60.3 mmol) of H-MeLeu-Val-MeLeu-Ala-OBzl (**20**), and 200 ml of $CHCl_3$ (precooled to –20°; stirring for 20 h at –20°). After washing with HCl and reextraction with CH_2Cl_2, the combined org. phase was washed twice with 200 ml of sat. $NaHCO_3$ soln., the aq. phases were extracted with 200 ml of CH_2Cl_2 and the combined org. phases dried (K_2CO_3) and evaporated. The residue (48.4 g) was chromatographed (1 kg of silica gel, 2.5% MeOH/CH_2Cl_2, then 7% MeOH/CH_2Cl_2): 9.9 g (20.6%) of **21**. $[\alpha]_D^{20} = -124$ (c = 1.0, $CHCl_3$). M.p. (Et_2O/hexane) 77–80°. The starting materials **19** and **20** could be recovered. ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 170°): 0.80–0.90 (*m*, 7Me); 1.20 (*d*, J = 6, Me–C(2.2)); 1.31 (*d*, J = 6, Me–C(2.6)); 1.36 (*s*, *t*-Bu); 1.50, 1.70 (2*m*, 2H–C(3.1), 2H–C(3.3), 2H–C(3.5), H–C(4.3), H–C(4.5)); 2.02 (*m*, H–C(3.4)); 2.86, 2.90, 2.95 (3*s*, Me–N(2.2), Me–N(2.3), Me–N(2.5)); 4.37 (2*m*, H–C(2.1), H–C(2.6)); 4.60 (*m*, H–C(2.4)); 4.83 (*m*, H–C(2.3); single evident change compared with MeAla^2 diastereoisomer (H–C(2.3) at 4.92)); 4.92 (*m*, H–C(2.5)); 5.11 (*s*, PhCH_2); 5.30 (*m*, H–C(2.2)); 5.28 (br. *s*, H–N(2.1)); 6.92 (br. *s*, H–N(2.4) or H–N(2.5)); 7.3 (*s*, *Ph*CH$_2$, H–N(2.5) or H–N(2.4)). FAB-MS: 803 (MH$^+$), 703 ([MH – Boc]$^+$), 624 ([M – Ala – OBz]$^+$), 524 ([624 – Boc]$^+$). Anal. calc. for $C_{42}H_{70}N_6O_9$ (803.061): C 62.8, H 8.8, N 10.5, O 17.9; found: C 62.3, H 9.0, N 10.1, O 18.5.

L-*2-Aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*H-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **22**). At –20°, 7.4 g (9.22 mmol) of **21** (precooled to –20°) were dissolved in 100 ml of CF_3COOH (precooled to –20°) and stirred for 3 h. The cold mixture was poured onto ice/H_2O containing $NaHCO_3$ (120 g), then 500 ml of CH_2Cl_2 were added, and the mixture was extracted. The aq. phase was reextracted twice with 200 ml of CH_2Cl_2, the combined org. phase dried (Na_2SO_4), and evaporated, and the residue (6.5 g) chromatographed (380 g of silica gel, 2.5, 5, 7, and 10% MeOH/CH_2Cl_2): 4.3 g (66%) of **22**. $[\alpha]_D^{20} = -70.8$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.89 (*m*, Me–C(3.1), 2Me–C(4.3), 2Me–C(3.4), 2Me–C(4.5)); 1.21 (*d*, J = 6, Me–C(2.2)); 1.32 (*d*, J = 6, Me–C(2.6)); 1.52, 1.62, 1.72 (3*m*, 2H–C(3.1), 2H–C(3.3), H–C(4.3), 2H–C(3.5), H–C(4.5)); 2.05 (*m*, H–C(3.4)); 2.62 (br. *s*, 2H–N(2.1)); 2.90 (*s*, 6H); 2.97 (*s*, Me–N(2.2), Me–N(2.3), Me–N(2.5)); 3.69 (*m*, H–C(2.1)); 4.40 (*m*, H–C(2.6)); 4.60 (*m*, H–C(2.3)); 4.88 (*m*, H–C(2.3)); 4.95 (*m*, H–C(2.5)); 5.11, 5.16 (2*d*, J = 9, PhCH_2); 5.32 (*m*, H–C(2.2)); 6.95, 7.30 (2 br. *s*, H–N(2.4), H–N(2.6)); 7.32 (*s*, *Ph*CH$_2$). FAB-MS: 703 (M^+). Anal. calc. for $C_{37}H_{62}N_6O_7$ (702.937): C 63.2, H 8.9, N 12.0, O 15.9; found: C 62.8, H 8.6, N 11.6, O 16.4.

N-*(* tert-*Butyloxycarbonyl)*-*[(2*S,*3*R,*4*R,*6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc-MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **24**). To a soln. of 2.27 g (7.55 mmol) of Boc-MeBmt-OH (**23**) in 100 ml of THF were added 0.9 g (9 mmol, 1.0 ml) of MeMorph, 2.24 g (16.6 mmol) of benzotriazol-1-ol (BtOH, 2.69 g of H_2O/BtOH 13:87 were dehydrated by azeotropic distillation of H_2O with 2 50-ml portions of toluene), 5.3 g (7.55 mmol) of **22**, and 1.87 g (9 mmol) of DCCI. The mixture was stirred for 20 h at r.t. under N_2, diluted with 500 ml of CH_2Cl_2 and washed with 150 ml of sat. $NaHCO_3$ soln. The aq. phase was reextracted with 200 ml of CH_2Cl_2, the combined org. phase dried (Na_2SO_4) and evaporated, the residue triturated with 100 ml of Et_2O, the Et_2O soln. filtered (removal of insoluble urea derivative of DCCI) and evaporated, and the residue (7.3 g) chromatographed (380 g of silica gel, 2% MeOH/CH_2Cl_2) to yield 6.12 g of foam which was rechromatographed (360 g of silica gel, hexane/AcOEt/acetone 45:45:10): 4.8 g (76%) of **24**. $[\alpha]_D^{20} = -98$ (c = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.80–0.90 (*m*, 8 Me); 1.22 (*d*, J = 6, Me–C(2.3)); 1.32 (*d*, J = 6, Me–C(2.7)); 1.42 (*s*, *t*-Bu); 1.50, 1.56, 1.70, 1.85 (4*m*, H–C(4.1), H–C(5.1), 2H–C(3.2), 2H–C(3.4), H–C(4.4), 2–H–C(3.6), H–C(4.6)); 1.60 (*d*, J = 3, Me–C(7.1)); 2.04 (*m*, H–C(3.5)); 2.28 (*d*, J = 9, H–C(5.1)); 2.87, 2.89, 2.91, 2.97 (4*s*, Me–N(2.1), Me–N(2.3), Me–N(2.4), Me–N(2.6)); 3.88 (*m*, H–C(3.1), OH–C(3.1)); 4.40 (*t*, J = 6, H–C(2.7)); 4.53 (*d*, J = 5, H–C(2.1)); 4.60 (*t*, J = 6, H–C(2.5)); 4.75 (*m*, H–C(2.2)); 4.82 (*m*, H–C(2.4)); 4.95 (*m*, H–C(2.6)); 5.09, 5.14 (2*d*, J = 9, PhCH_2); 5.42 (*m*, H–C(6.1), H–C(7.1)); 5.45 (*m*, H–C(2.3)); 6.92 (2H); 7.28 (2 br. *s*, H–N(2.2), H–N(2.5), H–N(2.7)); 7.32 (*s*, *Ph*CH$_2$). FAB-MS: 986 (MH$^+$, $C_{52}H_{87}N_7O_{11}$), 886 ([MH – Boc]$^+$), 807 ([M – Ala–OBzl]$^+$), 581 ([M – (Val–MeLeu–Ala–OBzl)]$^+$), 454 ([Boc–MeBmt–Abu–D-MeAla]$^+$).

*(2*S,*3*R,*4*R,*6*E*)-3-Hydroxy-4-methyl-2-(methylamino)oct-6-enoyl*-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*H-MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **25**). As described for **22**, with 4.8 g (4.87 mmol) of **24** and 30 ml of CF_3COOH. Workup with ice/H_2O containing 40 g of $NaHCO_3$ and 3 × 200 ml of CH_2Cl_2. The residue (4.37 g) was chromatographed (360 g of silica gel, 2 then 5% MeOH/CH_2Cl_2): 3.5 g (81%) of **25**. $[\alpha]_D^{20} = -128.4$ (c = 1.0, $CHCl_3$). ^{1}H-NMR

((D$_6$)DMSO, 360 MHz, 180°): 0.80–0.90 (*m*, 8 Me); 1.21 (*d*, *J* = 6, Me–C(2.3)); 1.31 (*d*, *J* = 6, Me–C(2.7)); 1.60 (*d*, *J* = 3, Me–C(7.1)); 1.50, 1.70, 1.85 (3*m*, H–C(4.1), H–C(5.1), 2H–C(3.2), 2H–C(3.4), H–C(4.4), 2H–C(3.6), H–C(4.6)); 2.04 (*m*, H–C(3.5)); 2.28 (*d*, *J* = 9, H–C(5.1)); 2.32 (*s*, Me–N(2.1)); 2.58 (br. *s*, H–N(2.1), OH–C(3.1)); 2.88, 2.92, 2.97 (3*s*, Me–N(2.3), Me–N(2.4), Me–N(2.6)); 3.45 (*m*, H–C(3.1)); 4.38 (*m*, H–C(2.7)); 4.58 (*t*, *J* = 6, H–C(2.5)); 4.77 (*m*, H–C(2.2)); 4.85 (*m*, H–C(2.4)); 4.95 (*m*, H–C(2.6)); 5.09, 5.14 (2*d*, *J* = 9, PhCH_2); 5.35 (*m*, H–C(2.3)); 5.43 (*m*, H–C(6.1), H–C(7.1)); 6.94, 7.28, 7.60 (3 br. *s*, H–N(2.2), H–N(2.5), H–N(2.7)); 7.32 (*s*, *Ph*CH$_2$). FAB-MS: 886 (M^+), 887 (MH^+). Anal. calc. for $C_{47}H_{79}N_7O_9$ (886.188): C 63.7, H 9.0, N 11.1, O 16.2; found: C 62.9, H 8.9, N 11.0, O 16.5.

N-*(*tert*-Butyloxycarbonyl)*-D-*alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc*-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **27**). At r.t., 754 mg (1.35 mmol) of Boc-D-Ala-MeLeu-MeLeu-MeVal-OH (**26**; for preparation, see CS synthesis [21a]) followed by 1.2 g (1.35 mmol) of **25** were dissolved in 20 ml of CH_2Cl_2. Then 0.3 ml (0.274 g, 2.7 mmol) of MeMorph and 1.2 g (2.7 mmol) of (BtO)P(Me$_2$N)$_3^+$PF$_6^-$ were added to the soln., and the mixture was stirred for 3 days at r.t. (TLC monitoring (silica gel, 5% MeOH/CHCl$_3$)). The resulting soln. was diluted with 200 ml of CH_2Cl_2, washed with 25 ml of 1N HCl then with 50 ml of sat. $NaHCO_3$ soln., and the aq. phases were extracted with 200 ml of CH_2Cl_2. The combined org. phase was dried (Na_2SO_4) and evaporated and the residue (2.7 g) chromatographed (220 g of silica gel, hexane/AcOEt/acetone 45:45:10): 1.45 g (75%) of **27**. $[\alpha]_D^{20} = -155$ (*c* = 1.0, CHCl$_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.76, 0.83 (2*d*, *J* = 6, 2Me–C(3.4)); 0.85–0.95 (*m*, 2Me–C(4.2), 2Me–C(4.3), Me–C(4.5), Me–C(3.6), 2Me–C(4.8), 2Me–C(3.9), 2Me–C(4.10)); 1.20 (*d*, *J* = 6, Me–C(2.1)); 1.25 (*d*, *J* = 6, Me–C(2.7)); 1.31 (*d*, *J* = 6, Me–C(2.11)); 1.38 (*s*, *t*-Bu); 1.60 (*d*, *J* = 3, Me–C(7.5)); 1.50, 1.55, 1.70 (3*m*, 2H–C(3.2), H–C(4.2), 2H–C(3.3), H–C(4.3), H–C(4.5), H–C(5.5), 2H–C(3.6), 2H–C(3.8), H–C(4.8), 2H–C(3.10), H–C(4.10)); 2.04 (*m*, H–C(3.9)); 2.28 (*m*, H–C(5.5), H–C(3.4)); 2.89, 2.92, 2.93, 2.94, 2.97 (5*s*, Me–N(2.2), Me–N(2.3), Me–N(2.4), Me–N(2.5), Me–N(2.7), Me–N(2.8), Me–N(2.10)); 3.92 (*t*, *J* = 3, H–C(3.5)); 4.42 (*t*, *J* = 6, H–C(2.11)); 4.48 (*m*, H–C(2.6)); 4.62 (*m*, H–C(2.9)); 4.76 (*m*, H–C(2.1)); 4.88 (*m*, H–C(2.8)); 4.98 (*m*, H–C(2.10)); 5.07 (*m*, H–C(2.5)); 5.15 (*d*, *J* = 3, PhCH_2); 5.17 (*d*, *J* = 9, H–C(2.4)); 5.35 (*m*, H–C(2.7)); 5.45 (*m*, H–C(6.5), H–C(7.5), H–C(2.2), H–C(2.3)); 5.90 (br. *s*, H–N(2.1)); 6.95–7.06, 7.29 (2 br. *s*, H–N(2.6), H–N(2.9), H–N(2.11)); 7.35 (*s*, *Ph*CH$_2$). FAB-MS: 1424 (M^+). Anal. calc. for $C_{75}H_{129}N_{11}O_{15}$ (1424.916): C 63.2, H 9.1, N 10.8, O 16.8; found: C 63.0, H 9.3, N 10.7, O 17.4.

D-*Alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine* (H-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OH*; **29**). At −7°, 5.4 ml of 0.2N NaOH were added to a soln. of 1.4 g (1.0 mmol) of **27** in 30 ml of abs. EtOH (precooled). The mixture was allowed to stand for 16 h at −7° (ice box), then adjusted to pH 5 with 0.1N HCl, and evaporated. The aq. residue was diluted with 50 ml of H_2O and extracted 3 times with 100 ml of CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated and the residue (1.3 g) chromatographed (110 g of silica gel, 10% MeOH/CH_2Cl_2): 1.0 g (76%) of *Boc*-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala-OH* (**28**). The latter was added as a powder at −20° to 5 ml of CF_3COOH (precooled) and stirred for 2 h at −20°. The soln. was poured onto ice/H_2O containing $NaHCO_3$ (10 g), the mixture extracted 3 times with 100 ml of CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the residue (0.92 g) chromatographed (110 g of silica gel, 15% MeOH/CH_2Cl_2): 0.7 g (83%) of **29**. Pale yellow foam. $[\alpha]_D^{20} = -154.6$ (*c* = 1.0, CHCl$_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.75, 0.82 (2*d*, *J* = 6, 2Me–C(3.4)); 0.82–0.95 (*m*, 2 Me–C(4.2), 2Me–C(4.3), Me–C(4.5), Me–C(3.6), 2Me–C(4.8), 2Me–C(3.9), 2Me–C(4.10)); 1.15, 1.24, 1.28 (3*d*, *J* = 6, Me–C(2.1), Me–C(2.7), Me–C(2.11)); 1.60 (*d*, *J* = 3, Me–C(7.5)); 1.50, 1.70, 1.80 (3*m*, 2H–C(3.2), H–C(4.2), H–C(3.3), H–C(4.3), H–C(4.5), H–C(5.5), 2H–C(3.6), 2H–C(3.8), H–C(4.8), 2H–C(3.10), H–C(4.10)); 2.05 (*m*, H–C(3.9)); 2.28 (*m*, H–C(5.5), H–C(3.4)); 2.88, 2.93 (6H), 2.94, 2.95, 2.97, 3.08 (6*s*, Me–N(2.2), Me–N(2.3), Me–N(2.4), Me–N(2.5), Me–N(2.7), Me–N(2.8), Me–N(2.10)); 3.47 (*m*, H–C(2.1)); 3.78 (br. *s*, OH–C(3.5)); 3.93 (*t*, *J* = 3, H–C(3.5)); 4.20 (*m*, H–C(2.11)); 4.62 (*t*, *J* = 6, H–C(2.9)); 4.85 (*m*, H–C(2.6), H–C(2.5)); 4.97 (*m*, H–C(2.8)); 5.03 (*m*, H–C(2.10)); 5.16 (*d*, *J* = 9, H–C(2.4)); 5.33 (*m*, H–C(2.7)); 5.40, 5.47 (2*m*, H–C(6.5), H–C(7.5), H–C(2.2), H–C(2.3)); 7.0 (br. *s*, H–N(2.6), H–N(2.9), H–N(2.11)); 2.80–3.15 (br. *s*, H–N(2.1), H_2O). FAB-MS: 1235 (MH^+), 1234 (M^+). Anal. calc. for $C_{63}H_{115}N_{11}O_{13}$ (1234.685): C 61.3, H 9.4, N 12.5, O 16.8; found: C 60.9, H 9.5, N 12.4, O 17.1.

Cyclo-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]-L-*2-aminobutyryl*-N-*methyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*] (*Cyclo-(MeBmt-Abu*-D-*MeAla-MeLeu-Val-MeLeu-Ala*-D-*Ala-MeLeu-MeLeu-MeVal-)*; [D-*MeAla*^{3}*]CS*; **2a**). To a soln. of 0.7 g (0.56 mmol) of **29** in 2.4 l of CH_2Cl_2 were added, with vigorous stirring, 0.28 g

(2.24 mmol) of 4-(dimethylamino)pyridine in 10 ml of CH_2Cl_2 and 0.27 ml of a soln. of 180 mg (1.7 mmol; 3 equiv.) of $(PrPO_2)_3$ in 180 mg of CH_2Cl_2 (50% (*w/w*) soln. in CH_2Cl_2). The mixture was stirred for 3 days at r.t. (TLC (silica gel, 5% MeOH/$CHCl_3$): some **29** remaining). The soln. was evaporated and the residue chromatographed (110 g of silica gel, 4% MeOH/CH_2Cl_2) to yield 0.46 g of product which was chromatographed again (110 g of silica gel, AcOEt/acetone/hexane 7:2:1): 301 mg (43%) of crude **2a**, $[\alpha]_D^{20} = -204$ (*c* = 1.0, $CHCl_3$), which was crystallized from $(i\text{-}Pr)_2O$ to yield 170 mg of **2a**. M.p. 194–197°. $[\alpha]_D^{20} = -215.5$ (*c* = 1.0, $CHCl_3$). Powder-diffraction diagram of **2a** (crystals from acetone) by the method of [29] gave the same line pattern and distances as natural CS [21a]. [D-MeAla^3]CS (**2a**) crystallizes as cyclosporin A (CS) and cyclosporin G in modification A_3 (film of **2a** No. 7993 (22.1.1985) to be compared with film 7041 (CSG) and films 5418 (nat. CS) and 5419 (synth. CS) [21]). For selected NMR data and comparisons, see *Table 2*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.70 (*d*, *J* = 6, Me–C(4.1)); 0.80–1.15 (*m*, Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.27 (*d*, *J* = 6, Me–C(2.8)); 1.36 (*d*, *J* = 6, Me–C(2.7)); 1.42 (*d*, *J* = 6, Me–C(2.3)); 1.62 (*d*, *J* = 3, Me–C(7.1)); 1.45, 1.70, 2.10 (3*m*, H–C(4.1), 2 H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6), 2 H–C(3.9), H–C(3.5), H–C(3.11), H–C(4.9), H–C(4.10)); 2.68, 2.70 (2*s*, Me–N(2.10), Me–N(2.11)); 3.10, 3.11 (2*s*, Me–N(2.4), Me–N(2.9)); 3.27, 3.29 (2*s*, Me–N(2.3), Me–N(2.6)); 3.50 (*s*, Me–N(2.1)); 3.74 (*m*, H–C(3.1)); 3.95 (*d*, *J* = 6, OH–C(3.1)); 4.54 (*m* = *t*, *J* = 6, H–C(2.7)); 4.64 (*t*, *J* = 8, H–C(2.5)); 4.83 (*t*, *J* = 6, H–C(2.8)); 4.94 (*m*, H–C(2.3), H–C(2.6)); 5.07 (*m*, H–C(2.2), H–C(2.10)); 5.13 (*d*, *J* = 12, H–C(2.11)); 5.29 (*dd*, *J* = 12, 4, H–C(2.9)); 5.34 (*m*, H–C(6.1), H–C(7.1)); 5.52 (*d*, *J* = 4, H–C(2.1)); 5.71 (*dd*, *J* = 12, 4, H–C(2.9)); 7.15 (*d*, *J* = 6, H–N(2.8)); 7.48 (*d*, *J* = 6, H–N(2.5)); 7.61 (*d*, *J* = 6, H–N(2.7)); 7.92 (*d*, *J* = 8, H–N(2.2)). FAB-MS: 1216 (M^+), 1217 (MH^+), 1104 ($[MH - 113]^+$, $[M - OCHCH(Me)CH_2CH{=}CH(Me)]^+$). Anal. calc. for $C_{63}H_{113}N_{11}O_{12}$ (1216.659): C 62.2, H 9.4, N 12.7, O 15.8; found: C 61.7, H 9.6, N 12.5, O 15.9.

Note: Separation of [D-MeAla^3]CS (**2a**) from [MeAla^3]CS (**2b**) on TLC (silica gel) was achieved by using AcOEt/hexane/acetone 4.5:4.5:1 or CH_2Cl_2/MeOH 95:5. The D-form is less polar than the L-form using these eluents. Separation by LC (silica gel) was successful using 4% MeOH/CH_2Cl_2.

7. *Synthesis of [MeAla^3]CS* (**2b**). N-*(*tert*-Butyloxycarbonyl)*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc-MeAla-MeLeu-Val-MeLeu-Ala-OBzl;* **31**). As described for **18**, with 10.0 g (49.3 mmol) of Boc-MeAla-OH (**30**), 200 ml of $CHCl_3$, 6.6 ml (1.1 equiv., 54.2 mmol) of pivaloyl chloride, 12.0 ml (2.2 equiv., 108.5 mmol) of MeMorph (stirring for 3 h), 26.3 g (49.3 mmol) of **20**, and 200 ml of $CHCl_3$ (stirring for 24 h at –20°; TLC monitoring (10% MeOH/$CHCl_3$)). After washing with 1n HCl (300 ml) and reextraction with CH_2Cl_2, workup proceeded as described for **21**. The residue (45.0 g) was chromatographed (0.8 kg of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2): 29.6 g (83.6%) of **31**. $[\alpha]_D^{20} = -157$ (*c* = 1.0, $CHCl_3$). White foam. ^{1}H-NMR ((D_6)DMSO, 360 MHz, 150°): 0.80–0.90 (6*d*, *J* ≈ 6, 2 Me–C(4.2), 2 Me–C(3.3). 2 Me–C(4.4)); 1.23 (*d*, *J* = 6, Me–C(2.1)); 1.31 (*d*, *J* = 8, Me–C(2.5)); 1.40 (*s*, *t*-Bu); 1.50, 1.65, 1.70 (3*m*, 2 H–C(3.2), 2 H–C(3.4), H–C(4.2), H–C(4.4)); 2.03 (*m*, H–C(3.3)); 2.70, 2.88, 2.92 (3*s*, Me–N(2.1), Me–N(2.2), Me–N(2.4)); 4.35 (*t*, *J* = 8, H–C(2.5)); 4.60 (*t*, *J* = 6, H–C(2.1)); 4.90 (*m*, H–C(2.2), H–C(2.3), H–C(2.4)); 5.08, 5.12 (2*d*, *J* = 12, PhCH_2); 6.95 (*m*, H–N(2.3) or H–N(2.5)); 7.3 (*s* + *m*, Ph, H–N(2.3) or H–N(2.5)). FD-MS: 718 (M^+), 617 ($[M - Boc]^+$). Anal. calc. for $C_{38}H_{63}N_5O_8$ (717.955): C 63.6, H 8.8, N 9.8, O 17.8; found: C 64.2, H 9.3, N 9.3, O 18.4.

N-*Methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*H-MeAla-MeLeu-Val-MeLeu-Ala-OBzl;* **32**). As described for **22**, with 29.5 g (41.0 mmol) of **31** and 150 ml of CF_3COOH (stirring for 20 h at –20°; TLC monitoring (10% MeOH/$CHCl_3$)). Workup with ice/H_2O containing excess sat. $NaHCO_3$ soln., reextraction with 500 ml of CH_2Cl_2. The residue (32.5 g) was chromatographed (silica gel (900 g), 3% MeOH/CH_2Cl_2): 19.5 g (77.1%) of **32**. White foam. $[\alpha]_D^{20} = -172.8$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 180°): 0.80–0.95 (6*d*, *J* ≈ 6, 2 Me–C(4.2), 2 Me–C(3.3), 2 Me–C(4.4)); 1.15 (*d*, *J* = 6, Me–C(2.1)); 1.31 (*d*, *J* = 6, Me–C(2.5)); 1.50 (*m*, 2 H–C(3.2), 2 H–C(3.4)); 1.73 (*m*, H–C(4.2), H–C(4.4)); 2.2 (*m*, H–C(3.3)); 2.23 (*s*, Me–N(2.1)); 2.50 (br. *s*, H–N(2.1)); 2.88, 2.93 (2*s*, Me–N(2.2), Me–N(2.4)); 3.58 (*m*, H–C(2.1)); 4.40 (*t*, *J* = 6, H–C(2.5)); 4.62 (br. *d*, H–C(2.3)); 4.85, 4.95 (2*m*, H–C(2.2), H–C(2.4)); 5.10, 5.15 (2*d*, *J* = 12, PhCH_2); 7.2–7.3 (*m*, H–N(2.3), H–N(2.5)); 7.35 (*s*, *Ph*CH_2). FD-MS: 618 (MH^+), 534, 482. Anal. calc. for $C_{33}H_{55}N_6O_6$ (617.836): C 64.2, H 9.0, N 11.3, O 15.5; found: C 63.7, H 9.4, N 11.2, O 16.1.

N-*(*tert*-Butyloxycarbonyl)*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl;* **33**). As described for **18**, but at –15°, with 6.4 g (31.6 mmol) of **16**, 100 ml of $CHCl_3$, 7.6 ml (69.5 mmol) of MeMorph, 4.2 ml (34.8 mmol) of pivaloyl chloride (stirring for 3 h), 19.5 g (31.6 mmol) of **32** and 200 ml of $CHCl_3$ (stirring for 20 h). After workup as described for **31**, the residue (39.2 g) was chromatographed (1 kg of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2): 18.6 g (73.5%) of **33**. White foam. $[\alpha]_D^{20} = -153.6$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 180°):

0.80–0.95 (*m*, 7 Me); 1.25, 1.31 (2*d*, Me–C(2.2), Me–C(2.6)); 1.39 (*s*, *t*-Bu); 1.51, 1.68 (2*m*, 2 H–C(3.1), 2 H–C(3.3), H–C(4.3), 2 H–C(3.5), H–C(4.5)); 2.02 (*m*, H–C(3.4)); 2.85, 2.90, 2.95 (3*s*, Me–N(2.2), Me–N(2.3), Me–N(2.5)); 4.38 (2*m*, H–C(2.1), H–C(2.6)); 4.60 (*t*, *J* = 6, H–C(2.4)); 4.92 (2*m*, H–C(2.3)); 4.93 (*m*, H–C(2.5)); 5.10, 5.15 (2*d*, *J* = 9, PhCH_2); 5.33 (*m*, H–C(2.2)); 5.80 (br.*s*, H–N(2.1)); 6.92, 7.30 (2 br. *s*, H–N(2.4), H–N(2.6)); 7.30 (*s*, *Ph*CH_2). FD-MS: 803 (M^+), 703 ([*M* – Boc]$^+$), 645, 531, 490. Anal. calc. for $C_{42}H_{70}N_6O_9$ (803.061): C 62.8, H 8.8, N 10.5, O 17.9; found: C 62.2, H 9.2, N 9.9, O 19.0.

L-*2-Aminobutyryl*-N-*methyl*-L-*alanyl*-*N-methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*H-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl;* **34**). As described for **22**, with 10.0 g (12.5 mmol) of **33** and 100 ml of CF_3COOH (stirring for 18 h). After workup as described for **32**, the residue (9.0 g) was chromatographed (500 g of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2). 5.8 g (68%) of **34**. White foam. $[\alpha]_D^{20} = -172.0$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.85–0.92 (*m*, Me–C(3.1), 2 Me–C(4.3), 2 Me–C(3.4), Me–C(4.5)); 1.22 (*d*, *J* = 6, Me–C(2.2)); 1.32 (*d*, *J* = 6, Me–C(2.6)); 1.42, 1.52, 1.70 (3*m*, 2 H–C(3.1), 2 H–C(3.3), 2 H–C(3.5), H–C(4.3), H–C(4.5)); 2.05 (*m*, H–C(3.4)); 2.85 (*s*, Me–N(2.2)); 2.92 (*s*, Me–N(2.3), Me–N(2.5)); 3.56 (*t*, *J* = 6, H–C(2.1)); 4.38 (*t*, *J* = 6, H–C(2.6)); 4.60 (*t*, *J* = 6, H–C(2.4)); 4.90, 4.92 (2*t*, *J* = 6, H–C(2.3), H–C(2.5)); 5.11, 5.16 (2*d*, *J* = 9, PhCH_2); 5.32, 5.38 (*dd*, *J* = 6, H–C(2.2)); 6.95, 7.28 (2*m*, H–N(2.4), H–N(2.6)); 7.32 (*s*, *Ph*CH_2). FD-MS: 703 (M^+), 645, 448, 314. Anal. calc. for $C_{37}H_{62}N_6O_7$ (702.943): C 63.2, H 8.9, N 12.0, O 15.9; found: C 62.7, H 9.1, N 11.7, O 16.5.

N,O-*Isopropylidene-[(2*S,*3*R,*4*R,*6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* ((N,O-*Isopropylidene*)-*MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **36**). For the preparation of (*N,O*-isopropylidene)MeBmt-OH (**35**), see [21a] (p. 520). A soln. of 5 mmol of **35**, freshly prepared from 1.2 g (5.0 mmol) of H-MeBmt-OH in 20 ml of acetone, was diluted with 100 ml of THF, and 5.5 ml (5.0 mmol) of MeMorph were immediately added. Then 3.3 g of **34** in 100 ml of THF containing 1.6 g (10.0 mmol) of BtOH were added, together with 1.1 g (5.2 mmol) of DCCI. The mixture was stirred for 3 days at 20° under moisture exclusion. Workup as described for **24** (washing twice with 200 ml of sat. $NaHCO_3$ soln., residue (13.5 g) triturating with 500 ml of Et_2O). The residue (8.8 g) was chromatographed (500 g of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2): 4.0 g (89%) of **36**. $[\alpha]_D^{20} = -142$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.80–0.95 (*m*, Me–C(4.1), Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6)); 1.17 (*s*, OC(CH_3)$_2$N); 1.25 (*d*, *J* = 6, Me–C(2.3)); 1.30 (*d*, *J* = 6, Me–C(2.7)); 1.50, 1.70, 1.80 (3*m*, H–C(4.1), 2 H–C(5.1), 2 H–C(3.2), 2 H–C(3.4), H–C(4.4), 2 H–C(3.6), H–C(4.6)); 1.60 (*s*, 3 H–C(8.1)); 2.03 (*m*, H–C(3.5)); 2.25 (*s*, Me–N(2.1)); 2.85, 2.92, 2.97 (3*s*, Me–N(2.3), Me–N(2.4), Me–N(2.6)); 3.10 (*d*, *J* = 6, H–C(2.1)); 3.71 (*dd*, *J* = 6, 15, H–C(3.1)); 4.40 (*m*, H–C(2.7)); 4.60 (*m*, H–C(2.3)); 4.75 (*m*, H–C(2.2)); 4.90 (*m*, H–C(2.4), H–C(2.6)); 5.09, 5.14 (2*d*, *J* = 9, PhCH_2); 5.35 (*m*, H–C(2.3)); 5.42 (*m*, H–C(6.1), H–C(7.1)); 6.88, 7.24, 7.48 (3 br. *d*, *J* ≈ 6, H–N(2.2), H–N(2.5), H–N(2.7)); 7.34 (*s*, *Ph*CH_2). FD-MS: 926 (M^+). Anal. calc. for $C_{50}H_{83}N_7O_9$ (926.249): C 64.8, H 9.0, N 10.6, O 15.6; found: C 64.9, H 9.4, N 10.5, O 15.9.

*[(2*S,*3*R,*4*R,*6*E*)-3-Hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*H-MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **37**). A soln. of 4.0 g (4.3 mmol) of **36** in 100 ml of MeOH was stirred for 20 h at r.t. in the presence of 6.0 ml of 1N HCl (TLC monitoring (silica gel, $CHCl_3$/MeOH 19:1)). After neutralization with solid $NaHCO_3$, the solvent was evaporated completely, at < 30° to avoid transesterification with MeOH. Then 100 ml of H_2O were added. The H_2O was extracted twice with 200 ml of CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the residue (6.0 g) chromatographed (350 g of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2): 2.9 g (76%) of **37**. $[\alpha]_D^{20} = -153.5$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 360 MHz, 180°): 0.80–0.98 (*m*, 8 Me); 1.21, 1.31 (2*d*, *J* = 6, Me–C(2.3), Me–C(2.7)); 1.55, 1.75, 1.85 (3*m*, H–C(5.1), H–C(4.1), 2 H–C(3.2), 2 H–C(3.4), 2 H–C(3.6), H–C(4.6)); 1.60 (*d*, *J* = 3, Me–C(7.1)); 2.05 (*m*, H–C(3.5)); 2.28 (*m*, H–C(5.1)); 2.35 (*s*, Me–N(2.1)); 2.90, 2.93, 2.99 (3*s*, Me–N(2.3), Me–N(2.4), Me–N(2.6)); 2.50–2.70 (br. *s*, H–N(2.1), OH–C(3.1)); 2.95 (*d*, *J* = 6, H–C(2.1)); 4.40 (*m*, H–C(2.7)); 4.60 (*m*, H–C(2.5)); 4.75, 4.80, 4.90 (3*m*, H–C(2.2), H–C(2.4), H–C(2.6)); 5.10, 5.14 (2*d*, *J* = 12, PhCH_2); 5.40 (*m*, H–C(6.1), H–C(7.1), H–C(2.3)); 7.05, 7.20, 7.60 (3 br. *s*, H–N(2.2), H–N(2.5), H–N(2.7)); 7.30 (*s*, *Ph*CH_2). FD-MS: 886 (M^+). Anal. calc. for $C_{47}H_{79}N_7O_9$ (886.195): C 63.7, H 9.0, N 11.1, O 16.2; found: C 63.1, H 9.0, N 11.0, O 16.5.

N-(tert-*Butyloxycarbonyl*)-D-*alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*-*[(2*S,*3*R,*4*R,*6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine Benzyl Ester* (*Boc*-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OBzl*; **38**). As described for **27**, with 2.0 g (3.6 mmol) of Boc-D-Ala-MeLeu-MeLeu-MeVal-OH [26] (**26**), 2.9 g (3.3 mmol) of **37**, 200 ml of $CHCl_3$, 4 ml (3.3 mmol) of MeMorph, and 1.6 g (3.6 mmol) of (BtO)P(Me$_2$N)$_3^+$PF$_6^-$. For workup, the resulting soln. was evaporated and the residue (11.6 g) chromatographed (700 g of silica gel (60–200 μm), 5% MeOH/CH_2Cl_2): 0.5 g of **37** and 2.1 g (45%) of **38**. $[\alpha]_D^{20} = -190$ (*c* = 1.0,

Table 2. *^{13}C- and ^{1}H-NMR Data* [ppm] *of [D-MeAla^3]CS* (**2a**) *and [L-MeAla^3]CS* (**2b**) *Compared with Data of Cyclosporin A (CS), in $CDCl_3$* (assignments made with COSY, TOCSY, and ROESY techniques by *M. Ponelle, Sandoz Pharma Ltd.*)

	Atom numbering inside each amino-acid residue[a])	Residue num-bering[b])	CS		**2a**			**2b**		
			δ (^{13}C)	δ (^{1}H)	δ (^{13}C)	$\Delta\delta_c$ (CS – **2a**)	δ (^{1}H)	δ (^{13}C)	$\Delta\delta_c$ (CS – **2b**)	δ (^{1}H)
CO	1	5	173.07	–	174.41	–1.34	–	173.71	–0.64	–
CO	1	2	173.04	–	173.42	–0.38	–	173.19	–0.15	–
CO	1	8	172.87	–	173.55	–0.68	–	172.96	–0.09	–
CO	1	11	172.85	–	173.44	–0.59	–	172.58	0.27	–
CO	1	6	170.87	–	171.68	–0.81	–	171.79	–0.92	–
CO	1	3	170.50	–	175.53	–5.03	–	171.71	–1.21	–
CO	1	7	170.44	–	171.14	–0.70	–	171.12	–0.68	–
CO	1	9	169.75	–	170.38	–0.63	–	172.73	–2.98	–
CO	1	1	169.65	–	170.27	–0.62	–	170.58	–0.93	–
CO	1	10	169.41	–	170.11	–0.70	–	169.98	–0.57	–
CO	1	4	169.35	–	170.04	–0.69	–	169.44	–0.09	–
CH	6	1	129.68	5.36	129.67	0.01	5.32	130.00	–0.32	5.18
CH	7	1	126.32	5.36	126.19	0.13	5.32	126.10	0.22	5.33
CH	3	1	74.74	3.83	74.93	–0.19	3.72	72.20	2.54	4.01
CH	2	1	58.75	5.48	59.07	–0.32	5.45	57.70	1.05	5.32
CH	2	11	57.93	5.15	57.84	0.09	5.11	58.50	–0.57	5.02
CH	2	10	57.54	5.08	57.61	–0.07	5.03	57.40	0.14	5.12
CH	2	4	55.51	5.32	55.49	0.02	5.28	58.20	–2.69	5.35
CH	2	5	55.39	4.67	55.49	–0.10	4.60	54.10	1.29	4.96
CH	2	6	55.31	4.99	55.28	0.03	4.92	54.80	0.51	5.22
CH	2	3	50.37	1.71, 3.19 (CH_2)	51.10	–0.73	4.93	48.20	2.17	5.34
CH	2	2	48.86	5.04	49.63	–0.77	5.01	51.90	–3.04	4.64
CH	2	7	48.69	4.51	48.55	0.14	4.51	48.50	0.19	4.45
CH	2	9	48.30	5.68	48.22	0.08	5.68	48.20	0.10	5.63
CH	2	8	45.20	4.83	45.10	0.10	4.81	44.30	0.90	4.82
CH_2	3	10	40.73	2.10, 1.22	40.65	0.08	2.1, 1.22	40.80	–0.07	2.08, 1.18
Me	N^2	3	39.40	3.39	31.56	7.84	3.22	30.20	9.20	3.15
CH_2	3	9	39.04	2.10, 1.26	38.56	0.48	2.06, 1.21	39.20	–0.16	2.09, 1.19
CH_2	3	6	37.41	2.08, 1.38	37.54	–0.13	2.02, 1.38	37.20	0.21	2.09, 1.27

CH_2	3	4	35.99	1.98, 1.62	35.81	0.18	1.97, 1.58	38.50	–2.51	1.88, 1.39
CH	4	1	35.99	1.62	36.30	–0.31	1.59	34.00	1.99	1.58
CH_2	5	1	35.63	2.38, 1.70	35.81	–0.18	2.41, 1.58	33.40	2.23	2.20, 1.72
Me	N^2	1	33.97	3.51	34.01	–0.04	3.48	31.70	2.27	3.38
Me	N^2	6	31.53	3.27	31.61	–0.08	3.24	31.40	0.13	3.10
Me	N^2	4	31.32	3.11	30.82	0.50	3.05	29.40	1.92	2.73
CH	3	5	31.17	2.42	31.07	0.10	2.42	33.40	–2.23	1.82
Me	N^2	10	29.83	2.7	29.75	0.08	2.68	29.80	0.03	2.66
Me	N^2	11	29.81	2.7	29.75	0.06	2.69	30.00	–0.19	2.65
Me	N^2	9	29.65	3.11	29.51	0.14	3.07	29.80	–0.15	3.17
CH	3	11	29.05	2.14	29.10	–0.05	2.11	28.90	0.15	2.08
CH	4	6	25.40	1.78	25.44	–0.04	1.73	24.90	0.50	1.88
CH_2	3	2	25.06	1.74, 1.62	25.01	0.05	1.70, 1.60	23.80	1.26	1.71, 1.5
CH	4	4	24.90	1.42	25.07	–0.17	1.38	24.40	0.50	1.47
CH	4	9	24.70	1.34	24.62	0.08	1.30	24.80	–0.10	1.31
CH	4	10	24.55	1.46	24.45	0.10	1.47	24.60	–0.05	1.45
Me	5	9	23.87	0.93	23.89	–0.02	0.93	23.80	0.07	0.93
Me	5	6	23.85	1.01	23.78	0.07	0.91	21.50	2.35	0.78
Me	5	10	23.74	0.97	23.68	0.06	0.99	23.80	–0.06	0.99
Me	5	4	23.49	0.93	23.42	0.07	0.92	23.70	–0.21	0.95
Me	5	10	23.36	1.01	23.40	–0.04	0.99	23.40	–0.04	1.01
Me	5	6	21.93	0.81	21.88	0.05	0.81	19.40	2.53	0.83
Me	5	9	21.86	0.89	21.84	0.02	0.86	20.00	1.86	0.85
Me	5	4	21.18	0.85	21.03	0.15	0.83	22.90	–1.72	0.92
Me	4	11	20.26	0.85	20.31	–0.05	0.81	21.80	–1.54	0.84
Me	4	5	19.81	1.05	19.97	–0.16	1.00	22.80	–2.99	0.94
Me	4	11	18.75	0.97	18.70	0.05	1.06	18.60	0.15	0.87
Me	4	5	18.48	0.89	18.36	0.12	0.85	17.90	0.58	0.78
Me	3	8	18.19	1.26	18.19	0.00	1.22	17.80	0.39	1.24
Me	8	1	17.96	1.62	17.90	0.06	1.60	17.90	0.06	1.52
Me	Me–C(4)	1	16.76	0.73	16.80	–0.04	0.67	17.10	–0.34	0.88
Me	3	7	16.07	1.34	15.93	0.14	1.34	15.70	0.37	1.30
Me	4	2	9.93	0.85	9.90	0.03	0.82	10.50	–0.57	0.88
Me	3	3	–	–	13.87	–	1.38	15.40	–	1.42

[a]) CO(1)–CH(2)N–C(3)–C(4)–C(5)–C(6)–C(7)–C(8).

[b]) MeBmt is residue 1 and MeVal residue 11 (see *Scheme 1*).

$CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 170°): 0.75, 0.82 (*2d*, $J = 6$, 2 Me–C(3.4)); 0.85–0.98 (*m*, 12 Me); 1.20, 1.25, 1.31 (*3d*, $J = 6$, Me–C(2.1), Me–C(2.7), Me–C(2.11)); 1.38 (*s*, *t*-Bu); 1.60 (*d*, $J = 3$, Me–C(7.5)); 1.54, 1.61, 1.80 (*3m*, 2 H–C(3.2), H–C(4.2), 2 H–C(3.3), H–C(4.3), H–C(4.5), H–C(5.5), 2 H–C(3.6), 2 H–C(3.8), H–C(4.8), 2 H–C(3.10), H–C(4.10)); 2.05 (*m*, H–C(3.9)); 2.3 (*m*, 2 H–C(5.5), H–C(3.4)); 2.84, 2.90–2.96, 3.05 (*7s*, Me–N(2.2), Me–N(2.3), Me–N(2.4), Me–N(2.5), Me–N(2.7), Me–N(2.8), Me–N(2.10)); 3.95 (*m*, H–C(3.5), OH–C(3.5)); 4.40 (*m*, H–C(2.11)); 4.47 (*m*, H–C(2.1)); 4.60 (*m*, H–C(2.9)); 4.73 (*m*, H–C(2.6)); 4.95 (*m*, H–C(2.3), H–C(2.5), H–C(2.10)); 5.12 (*s*, PhCH_2); 5.14 (*d*, $J = 6$, H–C(2.4)); 5.35 (*m*, H–C(2.7)); 5.42 (*m*, H–C(6.5), H–C(7.5), H–C(2.2), H–C(2.8)); 5.85 (*d*, $J = 6$, H–N(2.1)); 6.87, 6.95, 7.25 (*3d*, $J = 6$, H–N(2.5), H–N(2.9), H–N(2.11)); 7.33 (*s*, *Ph*CH_2). FD-MS: 1424 (M^+), 1447 ($[M + Na]^+$), 1406 ($[M - H_2O]^+$). FAB-MS: 1424 (M^+). Anal. calc. for $C_{75}H_{129}N_{11}O_{15}$ (1424.929): C 63.2, H 9.1, N 10.8, O 16.8; found: C 63.3, H 9.2, N 10.8, O 16.9.

N-*(*tert*-Butyloxycarbonyl)*-D-*alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine* (*Boc*-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OH*; **39**). At 0°, 15.4 ml of 0.2N NaOH were added to a soln. of 3.6 g (2.5 mmol) of **38** in 77 ml of abs. EtOH (precooled). The mixture was allowed to stand for 20 h at –8° (TLC monitoring (silica gel, 10% MeOH/$CHCl_3$)), then adjusted to pH 5 with 1N HCl, and fully evaporated (H_2O bath at 40°). The amorphous residue was shaken with 200 ml of H_2O and 3 times with 300 ml of CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the residue (3.6 g) chromatographed (250 g of silica gel (60–200 μm), 10% MeOH/CH_2Cl_2): 2.5 g (76%) of **39**. $[\alpha]_D^{20} = -196$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 170°): 0.75, 0.85 (*2d*, $J = 6$, 2 Me–C(3.4)); 0.86, 0.95 (*2m*, 2 Me–C(4.2), 2 Me–C(4.3), Me–C(4.5), Me–C(3.6), 2 Me–C(4.8), 2 Me–C(3.9), 2 Me–C(4.10)); 1.18, 1.21, 1.23 (*3d*, $J = 6$, Me–C(2.1), Me–C(2.7), Me–C(2.11)); 1.38 (*s*, *t*-Bu); 1.61 (*d*, $J = 3$, Me–C(7.5)); 1.55, 1.70, 1.82 (*3m*, 2 H–C(3.2), H–C(4.2), 2 H–C(3.3), H–C(4.3), H–C(4.5), H–C(5.5), 2 H–C(3.6), 2 H–C(3.8), H–C(4.8), 2 H–C(3.10), H–C(4.10)); 2.05 (*m*, H–C(3.9)); 2.28 (*m*, H–C(3.4), 2 H–C(5.5)); 2.88 (*s*, MeN); 2.90 (*s*, MeN); 2.92 (*s*, 2 MeN); 2.95 (*s*, MeN); 2.97 (*s*, MeN); 3.05 (*s*, MeN); 3.92 (*t*, $J = 6$, H–C(3.5), OH–C(3.5)); 4.00 (*m*, H–C(2.11)); 4.45 (*t*, $J = 6$, H–C(2.1)); 4.60 (*m*, H–C(2.9)); 4.70 (*m*, H–C(2.6)); 4.90, 4.98 (*2m*, H–C(2.5), H–C(2.3), H–C(2.10)); 5.12 (*d*, $J = 6$, H–C(2.4)); 5.35 (*m*, H–C(2.7)); 5.41 (*m*, 3 CH); 5.45 (*m*, CH); 5.82 (*d*, $J = 6$, H–N(2.1)); 6.85 (br. *s*, 2 NH); 6.99 (br. *s*, NH). Note: the possible diastereoisomer containing D-MeVal instead of MeVal would be recognized at signals at 0.78 for Me–C(3.4) and at 5.08 for H–C(2.4). MS-FD: 1335 ($M H^+$), 1360 ($[M + Na]^+$). Anal. calc. for $C_{68}H_{123}N_{11}O_{15}$ (1334.803): C 61.2, H 9.3, N 11.5, O 18.0; found: C 60.4, H 9.1, N 11.3, O 18.5.

D-*Alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanine* (*H*-D-*Ala-MeLeu-MeLeu-MeVal-MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala-OH*; **40**). To 2.2 g (1.7 mmol) of **39** at –20°, 20 ml of CF_3COOH precooled to –20° were added with stirring. The clear soln. was stirred for further 20 h and the solvent evaporated at –20° (water-pump vacuum). The remaining oil was diluted with 200 ml of CH_2Cl_2 and shaken with sat. $NaHCO_3$ soln. (100 ml). The aq. phase was washed twice with 100 ml of CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the white foam chromatographed (180 g of silica gel, 20% MeOH/CH_2Cl_2): 0.7 g (35%) of **40**. Amorphous white foam. $[\alpha]_D^{20} = -220$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ((D_6)DMSO, 360 MHz, 180°): 0.78 (*d*, $J = 6$, Me–C(3.4)); 0.80–0.95 (*m*, 13 Me); 1.12 (*d*, $J = 6$, Me–C(2.1)); 1.23, 1.25 (*2d*, $J = 6$, Me–C(2.7), Me–C(2.11)); 1.50, 1.70, 1.85 (*3m*, 2 H–C(3.2), H–C(4.2), 2 H–C(3.3), H–C(4.3), H–C(4.5), 2 H–C(3.6), 2 H–C(3.8), H–C(4.8), 2 H–C(3.10), H–C(4.10), 2 H–C(5.5)); 1.60 (*s*, Me–C(7.5)); 2.05 (*m*, H–C(3.9)); 2.28 (*m*, 2 H–C(5.5)); 2.75 (br. *s*, Me–N(2.1)); 2.85 (*s*, MeN); 2.91, 2.95 (*2s*, 5 MeN); 3.08 (*s*, MeN); 3.77 (*m*, H–C(2.1)); 3.92 (*m*, H–C(3.5)); 3.99 (br. *s*, OH–C(3.5)); 4.61 (*m*, H–C(2.11)); 4.71 (*dd*, $J = 12, 6$, H–C(2.9)); 4.90, 4.96 (*2m*, H–C(2.6), H–C(2.8), H–C(2.5)); 5.60 (*d*, $J = 9$, H–C(2.4)); 5.45, 5.50 (*2m*, H–C(6.5), H–C(7.5), H–C(2.2), H–C(2.3), H–C(2.7), H–C(2.10)); 6.95, 7.02, 7.08 (3 br. *s*, H–N(2.6), H–N(2.9), H–N(2.11)); 7.1–7.6 (br., COOH). FD-MS: 1235 ($M H^+$). Anal. calc. for $C_{63}H_{115}N_{11}O_{13}$ (1234.685): C 61.3, H 9.4, N 12.5, O 16.8; found: C 60.5, H 9.1, N 11.8, O 17.2.

Cyclo{-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoyl]*-L-*2-aminobutyryl*-N-*methyl*-L-*alanyl*-N-*methyl*-L-*leucyl*-L-*valyl*-N-*methyl*-L-*leucyl*-L-*alanyl*-D-*alanyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*leucyl*-N-*methyl*-L-*valyl*} (*Cyclo-(MeBmt-Abu-MeAla-MeLeu-Val-MeLeu-Ala*-D-*Ala-MeLeu-MeLeu-MeVal); [MeAla³]-CS*; **2b**). To a soln. of 0.5 g (0.4 mmol) of **40** in 2 l of CH_2Cl_2 were added with vigorous stirring 0.2 g (1.6 mmol, **4** equiv.) of 4-(dimethylamino)pyridine and 0.13 g (0.2 ml, 3 equiv.) of $(PrPO_2)_3$. The clear colorless soln. was stirred for 3 days at r.t. excluding moisture, then concentrated to 50 ml, and chromatographed without workup (110 g of silica gel, 4% MeOH/CH_2Cl_2): 205 mg (42%) of **2b**. Not yet crystalline. $[\alpha]_D^{20} = -234$ (*c* = 1.0, $CHCl_3$). UV (MeOH): 196 nm ($\varepsilon^1 = 55.01\ l \cdot g^{-1} \cdot cm^{-1}$). IR ($CCl_4$): 3340, 3300 (sh), 1675, 1650–1620*s*, 990, 965 cm^{-1}. For

selected NMR data and comparison, see *Table 2*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.80–1.10 (*m*, Me–C(4.1), Me–C(3.2), 2 Me–C(4.4), 2 Me–C(3.5), 2 Me–C(4.6), 2 Me–C(4.9), 2 Me–C(4.10), 2 Me–C(3.11)); 1.27 (*d*, $J = 6$, Me–C(2.8)); 1.34 (*d*, $J = 6$, Me–C(2.7)); 1.45 (*d*, $J = 9$, Me–C(2.3)); 1.57 (*d*, $J = 6$, Me–C(7.1); 1.40, 1.70–2.30 (2*m*, H–C(4.4), 2 H–C(3.9), 2 H–C(3.10), 2 H–C(3.6), 2 H–C(3.4), H–C(4.1), H–C(4.9), 2 H–C(4.10), 2 H–C(3.2), H–C(4.6), H–C(3.5), 2 H–C(5.1), H–C(3.11)); 2.68, 2.69 (2*s*, Me–N(2.10), Me–N(2.11)); 2.76 (*s*, Me–N(2.4)); 2.85, 2.89, 2.98, 3.00, 3.02, 3.24 (6*s*, MeN signals of conformers); 3.14 (*s*, Me–N(2.6)); 3.18 (*s*, Me–N(2.3)); 3.20 (*s*, Me–N(2.9)); 3.40 (*s*, Me–N(2.1)); 4.05 (*m*, H–C(3.1)); 4.47 (*m*, H–C(2.7)); 4.66 (*m*, H–C(2.2)); 4.85 (*m*, H–C(2.8)); 4.99 (*m*, H–C(2.5)); 5.04 (*d*, $J = 12$, H–C(2.11)); 5.16 (*m*, H–C(2.10)); 5.26 (*m*, H–C(2.6), H–C(6.1)); 5.38 (*m*, H–C(7.1), H–C(2.3) irradiation at 5.38→*s* at 1.45 and 1.57); 5.35 (*m*, H–C(2.1), H–C(2.4)); 5.68 (*dd*, $J = 12, 4$, H–C(2.9)); 7.22 (*d*, $J = 6$, H–N(2.8)); 7.75 (*d*, $J = 6$, H–N(2.7)); 7.92 (*d*, $J = 6$, H–N(2.2)); 8.30 (*d*, $J = 6$, H–N(2.5)); 7.10, 8.18, 8.50, 8.89 (4*d*, $J = 6$, NH of conformer (10%)). FD-MS: 1216 (M^+), 1217 (MH^+). FD-MS: 1217 (MH^+), 1239 ($[M + 23\ (Na)]^+$), 1240 ($[MH + 23\ (Na)]^+$). Anal. calc. for $C_{63}H_{113}N_{11}O_{12}$ (1216.659): C 62.2, H 9.4, N 12.7, O 15.8; found: C 61.9, H 9.5, N 12.5, O 15.9.

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