119. Preparation of Oxazolidine-Containing Peptides: Unusual Effects in Rh^{III}-Catalyzed Acetalizations of Aldehydes with Urethane-Protected Serine and Threonine Esters and with Dipeptides Containing Serine or Threonine Residues at the N-Terminus

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The cyclization reaction of aldehydes with Z- and Boc-protected β-hydroxyamino-acid esters (*Tables 1* and *2*), or of dipeptides containing serine or threonine at the N-terminus (*Table 3*), to give oxazolidine derivatives, occurs in the presence of isopropyl orthoformate and catalytic amounts of $[Rh(MeCN)_3(triphos)](CF_3SO_3)_3$. The reaction may be carried out under kinetic or under thermodynamic control, so that the ratio of the two possible epimeric products can be changed. The protecting group can be removed from the 3-position of the oxazolidine ring, and the resulting NH group can be coupled with another amino acid. Thus, a new method for the preparation of peptides containing β-hydroxy-amino acid-derived oxazolidines ('pseudo-prolines') is available. *N*-Neopentyl-substituted tripeptides are also described.

Serine-Derived Oxazolidines and Transition-Metal Acetalization Catalysts. – Oxazolidines, prepared from the β-hydroxyamino acids serine and threonine, have found multiple uses in stereoselective syntheses [1–10]. They have been employed by one of our groups to synthesize α-branched analogs of serine and threonine, as well as other synthetically interesting building blocks [11–14], applying the principle of *self-regeneration of stereogenic centers* [15–17]. Not only have these amino acids shown themselves as useful building blocks in diastereoselective syntheses, but the concomitant mechanistic and structural investigations have led to better understanding of the role amide groups play in modern organic synthesis, as discussed in a recently published review article [18]. Following a totally different line of work, *Mutter et al.* showed that the solubility problems often encountered both in solid and solution-phase peptide synthesis can be overcome by incorporating serines, as oxazolidine derivatives ('pseudo-prolines'), thus preventing the formation of poorly soluble β-strands [19]. For this purpose, the pivalaldehyde acetal of serine methyl ester was used as a building block in an otherwise conventional peptide synthesis.

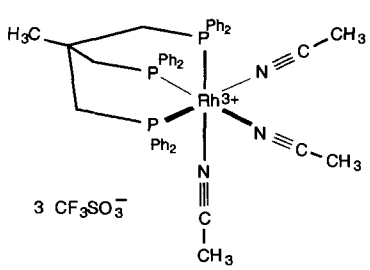
Recent work on transition-metal-catalyzed acetalization indicated that it might be possible to obtain oxazolidines directly from a given peptide. For over a decade, a

[1]) Part of the projected Ph. D. theses of *T. S.* and of *J. Q.*, ETH-Zürich. The authors gratefully acknowledge a stipend given to *T. S.* by the *Verband der Chemischen Industrie* (D–Frankfurt).

number of groups [20–25] have been interested in the application of cationic metallic complexes [26–31] for the preparation of acetals. Unlike protons, the transition-metal center may supply several 'binding sites for the substrate'. Thus, these catalysts can be expected and actually have been found to enhance reaction rates by entropic effects. Furthermore, by varying the ligands attached to the metal, the rate of interchange of other ligands is tunable.

Over the past few years, one of our groups has developed acetalization catalysts bearing the tripod ligand $CH_3C(CH_2PPh_2)_3$ using metals such as Ru [26–28], Rh [29–31], and with bidentate ligands such as $Ph_2PCH_2CH_2PPh_2$ with Pd, and Pt [31]. In several cases, these cations have proved to be clearly superior to the known *classical* acid catalysts of organic synthesis, such as simple mineral-acid derivatives, or acidic ion-exchange resin, or polymer-bound acids, or CF_3COOH. On the other hand, these metal catalysts may be poisoned by compounds containing certain functional groups, such as free amino groups, presumably by formation of stable metal-amine complexes.

Results. – In the present study, to avoid the problem of nitrogen-donor coordination, *N*-urethane-protected amino-acid and peptide derivatives were used, and the Rh and Ru complexes, **1** and **2**, respectively, were tested as catalysts. First, the simple methyl and



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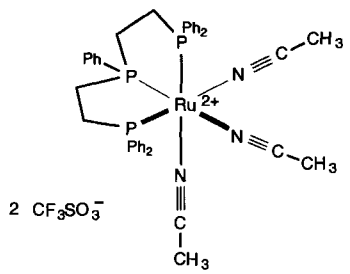

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benzyl α-amino-β-hydroxy-carboxylates **3**–**7**, which are either commercially available or can be readily prepared by standard procedures [32], were allowed to react with pivalaldehyde, giving the *cis*- or the *trans*-oxazolidines **8a**–**12a** and **8b**–**12b** as products (*Scheme 1*).

Z-Threonine-OMe (**5**) which gave a mixture of the corresponding oxazolidines **10a** and **10b** was used to optimize conditions (*Table 1*). Catalyst, solvent, temperature, reaction time, and drying agent were varied. Only the Rh catalyst **1** was active in this case, and 2 mol-% of it were generally used. To remove H_2O formed, an orthoformate ester was added. There is a tendency in such acetalizations for the formation of condensation products between the orthoester and the amino-alcohol, more so with the methyl and ethyl than with the isopropyl orthoformates. A cyclic orthoformic-acid derivative may actually be an intermediate in these acetalizations. In the present case, amide acetals of type **13** could be isolated, when the reaction was run at lower temperatures (refluxing CH_2Cl_2 or benzene at 35°) or, of course, when no aldehyde was added. In refluxing benzene or toluene, the yield of the pentane-soluble crude product was as high as 90% after filtration of the reaction mixture through *Celite*. The results obtained with different hydroxyamino-acid derivatives are presented in *Table 2*.

Scheme 1

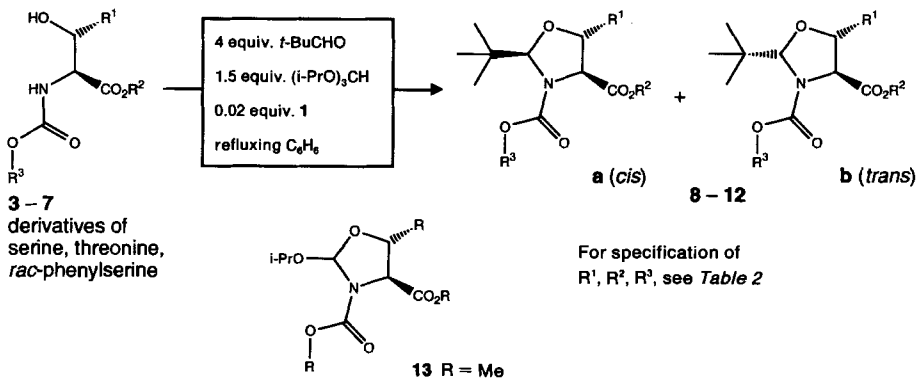


Table 1. *Optimization of the Preparation of Oxazolidine* **10** *from Z-Thr-OMe* (**5**). The yields refer to product isolated after flash chromatography. An 0.2 mol-% of **1** was used in all cases.

Catalyst	Solvent	Agent for dehydration	Temp.	Reaction time [h]	Ratio dipeptide/ aldehyde/$(RO)_3CH$	Yield [%] of **10**
1	PhH	$(i\text{-PrO})_3CH$	20°	96	1:2:1	0
1	CH_2Cl_2	Mol. sieves (4 Å)[a])	41°	24	1:2	0
1	CH_2Cl_2	$(i\text{-PrO})_3CH$	41°	48	1:2:1	0
1	PhH	$(i\text{-PrO})_3CH$	40°	33	1:2:1	0[b])
1	PhH	$(i\text{-PrO})_3CH$	80°	67	1:2:1	40
1	PhH	$(MeO)_3CH$	80°	85	1:3:1.5	22[c])
1	PhH	$(i\text{-PrO})_3CH$	80°	85	1:4:1.5	60
1	PhMe	$(i\text{-PrO})_3CH$	110°	24	1:3:1.5	69
1	PhH	$(i\text{-PrO})_3CH$	80°	24	1:4:1	75
1	PhH	$(i\text{-PrO})_3CH$	80°	85	1:4:1	60
2	PhH	$(i\text{-PrO})_3CH$	20°	168	1:2:1	0
2	PhH	$(i\text{-PrO})_3CH$	80°	48	1:2:1	0[d])

[a]) The molecular sieve was put into a perforated glass inlet in the gas phase underneath the cooling coil of the reflux condenser.

[b]) A *ca.* 1:1 mixture of epimers of the orthoester derivative of type **13** was obtained in 60% yield (after chromatographic purification; see *Exper. Part*).

[c]) The other major component of the product mixture was the orthoester derivative of type **13** with MeO instead of i-PrO.

[d]) The major product was again the i-PrO-oxazolidine of type **13**, obtained in 40% yield after flash chromatography.

The configurations of the oxazolidines **8**–**12** were derived from measurements of the nuclear *Overhauser* effect (NOE) in the ^{1}H-NMR spectra (see *Fig. 1* in the *Exper. Part*), by comparison of the NMR data with literature values for analogous products [11], and by an X-ray crystal structure of the threonine-derived (2*R*,4*S*,5*R*)-2-(*tert*-butyl)-3-(methoxycarbonyl)-5-methyloxazolidine-4-carboxylic acid[2]). There are several surprises:

[2]) This acid was previously described in [11]. The structure is in line with that of other *N*-acylated oxazolidines [18]: the *t*-Bu group occupies a *quasi*-axial position below the ring, and the acyl group resides on the other face of the ring on a pyramidalized ring N-atom. The authors thank *Florian Kühnle* for determining the crystal structure.

Table 2. *Oxazolidine Formation from Z-Protected β-Hydroxyamino-Acid Esters with Pivalaldehyde.* All reactions were carried out in refluxing benzene. The yields refer to product isolated after flash chromatography. An 0.2 mol-% of **1** was used in all cases.

Educt		Substituents in **3**–**12**			Reaction time [h]	Product		
		R^1	R^2	R^3		No.	Yield [%]	Ratio **a**/**b** *cis*/*trans*
Z-Ser-OMe	(**3**)	H	Me	Bn	24	**8**		80:20
					72	**8**	87	80:20
Z-Ser-OBn	(**4**)	H	Bn	Bn	24	**9**		19:81
					72	**9**	62	55:45
					144	**9**	53	76:24[a])
Z-Thr-OMe	(**5**)	Me	Me	Bn	24	**10**	75	9:91
					85	**10**	60	75:25[b])
Z-Thr-Bn	(**6**)	Me	Bn	Bn	12	**11**	87	4:96
					36	**11**	57	75:25[c])
rac-Z-PhSer-OMe	(**7**)	Ph	Me	Bn	72	**12**	39[d])	< 1:99

[a]) This *cis*/*trans* ratio did not change, when the epimeric mixture was heated at reflux in *o*-xylene (b.p. 143–145°) with **1** for another 12 h.

[b]) After heating the 75:25 mixture at reflux in *o*-xylene with **1** for another 12 h, a *cis*/*trans* ratio of 88:12 was obtained.

[c]) After heating the 75:25 mixture at reflux in *o*-xylene with **1** for another 11 h, a *cis*/*trans* ratio of 87:13 was obtained.

[d]) There is substantial formation of the dehydroamino-acid derivative by elimination of H_2O from phenylserine.

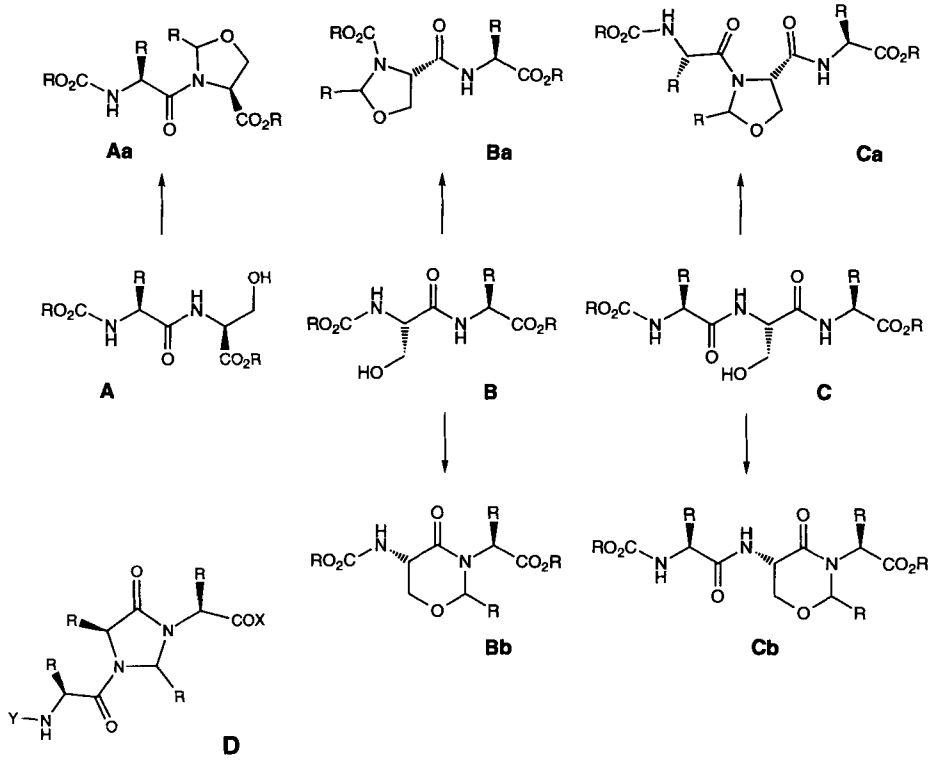
i) The products **8** and **9**, obtained from Z-serine methyl (**3**) and benzyl esters (**4**) after 24 h, have opposite configuration (*cis vs. trans*). *ii*) While the ratio of the epimers **8a** and **8b** formed from the methyl ester **3** does not change after an additional 48 h, the ratio of the analogous benzyl esters **9a** and **9b** reverses after 144 h. *iii*) The threonine and the phenylserine derivatives **5**–**7** give > 90% pure *trans*-oxazolidines **10**–**12** under kinetically controlled conditions. In previous work, it was found that 1:1 *cis*/*trans*-mixtures of *N*-unsubstituted oxazolidines give preferentially the *cis*-products upon formylation and methoxycarbonylation [11] [14] [33]. Similarly, thiazolidines derived from cysteine were found to give exclusively the *cis*-products upon benzyloxycarbonylation [34]. The structural information from X-ray analyses was used to interpret this stereoselectivity [18][3]).

The results described here show the distinctly different nature of the transition-metal catalyst as compared to protic-acid catalysts for acetalizations of simple serine and threonine derivatives.

The Rh^{3+}-catalyzed acetalization with dipeptides **A**, **B**, and tripeptides **C**, containing a serine or threonine residue at the C-terminal, N-terminal, or internal position were next tested. As outlined in *Scheme 2*, there are five different acetalization products, if one disregards cyclic acetals with rings which are larger than six-membered: the C-terminal serine moiety **A** can only give rise to an oxazolidine **Aa**; the dipeptide **B** with N-terminal

[3]) In the acetylation of a thiazolidine carboxylic acid it has been possible to obtain selectively the *trans*-isomer (Ac_2O/pyridine at r.t.), and under another set of conditions (Ac_2O/water at 100°) the corresponding *cis*-product was exclusively formed [35]. Due to the heterogeneous nature of the reaction under both conditions, no explanation was given for this interesting stereoselectivity.

Scheme 2



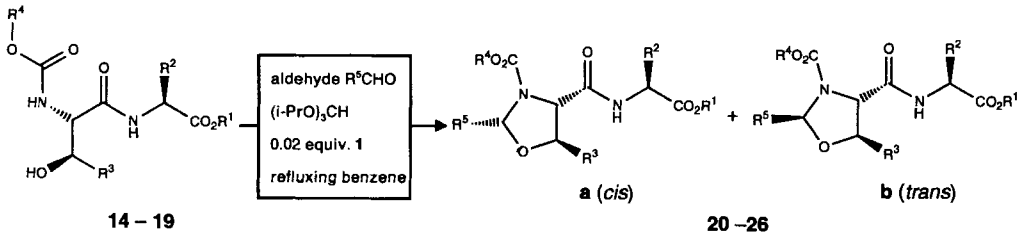
serine could cyclize either to an oxazolidine **Ba** *via* the serine ROCO-protected NH or to a 1,3-tetrahydrooxazine **Bb** *via* the NH of the neighboring amino acid; the tripeptide **C** could likewise lead to a five-membered ring **Ca** or a six-membered ring acetal **Cb**, depending upon whether the NH groups of the serine itself or of the C-terminal amino acid participate in the reaction. To the best of our knowledge, the formation of oxazolidines **Aa**, **Ba**, and **Ca** or of imidazolidinones of type **D** directly from peptides has never been observed[4]).

The derivatives **14**–**19** of dipeptides with N-terminal β-hydroxyamino-acid residues, Ac-Leu-Ser-OBn with a C-terminal serine, as well as Ac-Leu-Ser-Val-O(*t*-Bu) and Z-Ala-Ser-Val-OPr with an internal serine residue were prepared by standard procedures [32]; some of them have actually been used and described in a previous paper on an improved synthetic access to didehydro peptides [43]. For the acetalization experiments, isobutyraldehyde, pivalaldehyde, and benzaldehyde were used, employing the conditions found to give best results with the urethane protected serine and threonine esters men-

[4]) Acetalizations of carbonyl compounds with peptides involving the N-terminal amino groups are known [36]; *N*-acylation of the resulting imidazolidinones may be carried out with an activated amino acid [37]. For the preparation of imidazolidinones from amino-acid amides, see *e.g.*, the publications from one of our groups [38–42].

tioned above. The formation of a cyclic acetal, be it an oxazolidine or a tetrahydrooxazine, was not observed either with the dipeptide containing a C-terminal, or with the tripeptides containing an internal serine residue and pivalaldehyde. Thus, it can be concluded that peptidic NH groups and serine OH groups cannot form cyclic acetals under the influence of the tripod Rh catalyst **1**. Since the simple carbamate-protected serine and threonine derivatives **3**–**7** did form oxazolidines, it was not surprising to find that all the dipeptides **14**–**19** with i-BuOCO-, *t*-BuOCO-, and BnOCO-protected N-terminal serine and threonine residues cyclized to the corresponding acetals **20**–**26** with isobutyraldehyde, pivalaldehyde or benzaldehyde (see *Scheme 3* and *Table 3*). As can be seen from *Table 3*, the yields obtained with pivalaldehyde range from 40 to 80%. The

Scheme 3



For specification of R^1, R^2, R^3, R^4, and R^5, see *Table 3*.

reaction conditions employed were less suitable for benzaldehyde and isobutyraldehyde than for pivalaldehyde: product **26** derived from the former slowly decomposed in the reaction mixture, while the low boiling point (65°) of the latter aldehyde prevented the use of the usual reaction temperature (refluxing C_6H_6) and, therefore, either longer reaction times were required, or the reaction had to be carried out under pressure. These acetalizations of dipeptides **14**–**19** brought about by the transition-metal catalyst **1** cannot be carried out under acid-catalyzed conditions, as tested with compound **16**: treatment with 1.3 equiv. of *t*-BuCHO, 1.7 equiv. of $(i\text{-PrO})_3CH$ in the presence of 0.014 equiv. of $TsOH \cdot H_2O$ in boiling benzene gave no trace of product **23** after 12 h.

In many cases, only one diastereoisomer of the oxazolidine was detected. Mixtures of *cis*/*trans*-isomers **a** and **b** could be separated by flash chromatography on SiO_2. The configuration of the oxazolidines **21b**, **22b**, **23a**, **24a**, **25a** and **b**, and **26b** was again derived from NOE measurements (see *Fig. 2* in the *Exper. Part*[5])). The most striking observations are: *i*) while isobutyraldehyde gave *ca.* a 1:1 mixture of the two epimers **20a** and **b**, *cis*- or *trans*-products were formed diastereoselectively with pivalaldehyde and benzaldehyde. *ii*) The oxazolidines derived from the serine-containing dipeptides and pivalaldehyde have *trans*-configuration (**21b** and **22b**) when formed under kinetic control, if the *N*-protecting groups are Boc or i-BuOCO. However, with the corresponding Z-protected dipeptides **16** and **17**, the *cis*-products **23a** and **24a** are the only ones detected. *iii*) In the case of the Boc-protected dipeptide **22**, the mixture containing excess of *trans*-product could be converted to a mixture in which the apparently more stable

[5]) The determination of the configuration of the epimers **20a** and **b** was not possible, due to signal crowding in the chemical-shift regions to be examined.

Table 3. *Formation of Dipeptides Containing a Urethane-Protected Oxazolidine at the N-Terminus from Dipeptides with β-Hydroxyamino-Acid Moieties.* All reactions were carried out in refluxing benzene with $(i\text{-PrO})_3CH$ as dehydrating reagent and with catalyst **1**. The yields refer to materials isolated after chromatographic purification and separation of the *cis/trans*-isomers.

Educts			Substituents in **14–26**					Conditions		Product		
Dipeptide		Aldehyde	R^1	R^2	R^3	R^4	R^5	Reaction time [h]	Ratio dipeptide/ aldehyde/$(i\text{-PrO})_3CH$	No.	Yield [%]	Ratio **a**/**b** (*cis/trans*)
i-BuOCO-Ser-Val-OMe	(**14**)	i-PrCHO	Me	i-Pr	H	Me_2CHCH_2	i-Pr	16	1:5:1.6	**20**	28[a])	55:45 or 45:55[b])
i-BuOCO-Ser-Val-OMe	(**14**)	*t*-BuCHO	Me	i-Pr	H	Me_2CHCH_2	*t*-Bu	14	1:4:1.5	**21**	77	< 1:99
Boc-Ser-Val-OBn	(**15**)	*t*-BuCHO	Bn	i-Pr	H	*t*-Bu	*t*-Bu	12	1:3:15	**22**	71	11:89
								72	1:3:1.1	**22**	57	68:32[c])
Z-Ser-Val-OMe	(**16**)	*t*-BuCHO	Me	i-Pr	H	Bn	*t*-Bu	21	1:3:1.5	**23**	78	> 99:1
Z-Ser-Phe-OEt	(**17**)	*t*-BuCHO	Et	Bn	H	Bn	*t*-Bu	24	1:3:1.7	**24**	37	> 99:1
Z-Thr-Gly-OBn	(**18**)	*t*-BuCHO	Bn	H	Me	Bn	*t*-Bu	24	1:3:1.7	**25**	80	82:18
Z-Thr-Phe-O^{t}Bu	(**19**)	PhCHO	*t*-Bu	Bn	Me	Bn	Ph	17	1:3:1.6	**26**	25[d])	< 1:99

[a]) The reaction was run at 65°, the boiling point of i-PrCHO. Nevertheless, the starting material could not be converted completely in spite of the addition of more i-PrCHO after 8 h.

[b]) Not determinable by 'simple' NOE-techniques.

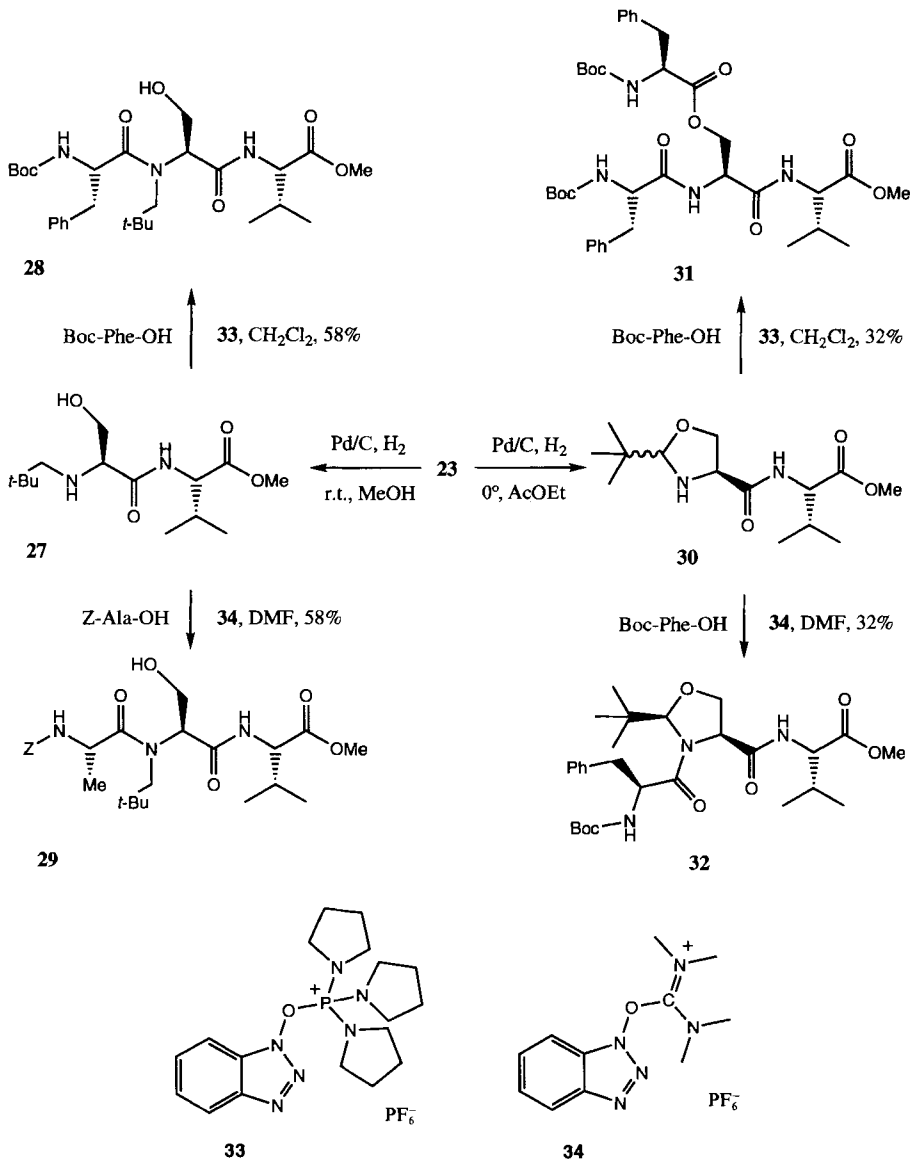
[c]) In toluene as the solvent, a *cis/trans* ratio of 83:17 was reached after 72 h.

[d]) Unidentified decomposition or side products are formed; after 24-h reaction time only 11% of **26** were isolated.

cis-isomer prevailed by increasing the reaction time and temperature. *iv*) The two oxazolidines **25** and **26**, derived from threonine-containing dipeptides and different aldehydes (pivalaldehyde *vs.* benzaldehyde), have the opposite configuration (*cis vs. trans*).

Thus, the Rh-tripod catalyst **1** provides products which are otherwise not accessible; furthermore, it shows a remarkable structure-stereoselectivity correlation which is not readily understood. The fact that a catalyst of this type keeps its activity in the presence of

Scheme 4



multifunctional substrates and products such as **3**–**26** is promising for further applications in complex organic syntheses. It is also worth pointing out that no epimerizations of stereogenic centers and no loss of Boc protecting groups[6]) were observed with the Rh-tripod triflate catalyst **1**, although the reaction temperature was 80°, and the mixture contained i-PrOH.

Since one could not generate an oxazolidine ring 'in the middle of a peptide', it was decided to take one of the oxazolidine-containing dipeptide derivatives, remove the carbamate protecting group, and attach an amino acid instead. For this purpose, the Z-protected compound **23** was chosen and attempts were made to debenzylate it hydrogenolytically under standard conditions (Pd/C, MeOH, room temperature). Surprisingly, **23** was converted quantitatively to a product, lacking the oxazolidine ring but still containing a *t*-Bu group, *i.e.*, the *N*-neopentyl dipeptide **27** (see *Scheme 4*). Accepting this gift of nature, this dipeptide was coupled with Boc-Phe-OH and Z-Ala-OH to the *N*-neopentyl tripeptides **28** and **29**, respectively[7]). This was only possible with the highly effective benzotriazole coupling reagents **33** and **34** which are known to be used with all kinds of hindered amino acids [47][8]). According to an NMR analysis, no racemization of the activated alanine or phenylalanine occurred in these reactions: configurationally pure products **28** and **29** were isolated in good yields. An aprotic solvent (AcOEt), a shorter reaction time, and a lower reaction temperature (0°) had to be chosen to prevent the reductive cleavage of the oxazolidine ring in **23** (see *Scheme 4*). The debenzylation product **30** was not easily handled and could not be purified by chromatography. It was formed in high yield as a 1:1 mixture of *cis*/*trans*-isomers (by NMR analysis), and the crude product was used for the coupling experiments with Boc-Phe-OH. With the phosphonium salt **33** ring-opening occurred, and the *N*- and *O*-acylated product **31** was isolated in modest yield after chromatographic purification; the formation of doubly coupled product could not be avoided by using just 1 equiv. of Boc-Phe-OH and the coupling reagent. With the uronium salt **34** the desired oxazolidine-containing tripeptide derivative **32** (*Scheme 4*) was formed as a single *cis*-isomer (as expected [11] [14] [33] [34]). Again, no epimerizations of stereogenic centers in the products **31** and **32** could be detected by NMR spectroscopy.

The tripeptide **32** containing a *pseudo-proline* residue might be used for the synthesis of larger peptides with the structural characteristics defined by *Mutter et al.* [19].

Experimental Part

General. All solvents were purchased from *Fluka AG* (*puriss.*). Urethane-protected amino-acid esters were purchased from *Senn Chemicals AG* and *Bachem Feinchemikalien AG*. Benzene was freshly distilled from P_2O_5 or dried over molecular sieve (4 Å) before use. Medium-pressure column chromatography (FC): *Merck* silica gel *60* (40–63 mm). TLC: silica gel *60 F254* (*Merck*), detection with Cl_2/TDM (*N,N,N′,N′*-tetramethyl-4,4′-methylenebis[aniline]) reagent [50] or a soln. of 25 g of phosphomolybdic acid and 10 g cerium(IV) sulfate in 60 ml

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[6]) In an acid-catalyzed reaction running at 80°, a Boc group would most likely be cleaved.

[7]) Although the formation or preparation of *N*-neopentylamino acids has been described in three papers [44–46], no amino acids of this type, incorporated in a peptide, or otherwise *N*-acylated, were found in a *CA* substructure search as of December 1993.

[8]) For peptide coupling, the phosphonium salt **33** was first proposed by *Castro* and coworkers [48], the uronium salt **34** by *Dourtoglou et al.* [49]. The mixed-anhydride method and the use of *p*-nitrophenol esters did not work for these couplings.

of conc. H_2SO_4 and 940 ml of H_2O. Anal. GC: *SE 54* (fused silica capillary column, 25 m, 0.25 mm), *Carlo Erba GC 6000 Chromatography*; injector temp. 250°, detector temp. 250° (FID); carrier gas, 0.5 bar H_2; temp. program: 80°, 20°/min till 250°. Optical rotations: *Perkin-Elmer-241* polarimeter. IR Spectra: *Perkin-Elmer-241* spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AM-400* (400 and 100 MHz, resp.), *Bruker-WM-300* (300 and 75 MHz, resp.), *Varian-Gem-200* (200 and 50 MHz, resp.); $CDCl_3$ solns., δ in ppm rel. to internal TMS, J in Hz and integrals (I) relative to each other. FAB-MS: *VG-ZAB2-SEQ* in a 3-nitrobenzyl-alcohol matrix; in m/z (% of basis peak). EI-MS: *VG-Tribrid* (70 eV). Peptide numbering according to [51].

*Methyl (2*R**,3*S**)-2-{[(Benzyloxy)carbonyl]amino}-3-hydroxy-3-phenylpropanoate* (**7**). A soln. of 7.00 g (30.2 mmol) of methyl (2*RS*,3*SR*)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride and 278 mg (3.02 mmol) of 4-(dimethylamino)pyridine in 90 ml of CH_2Cl_2 was cooled to −15°. Benzyloxycarbonyl chloride (4.31 ml, 30.2 mmol) and 5.17 ml (30.2 mmol) of Et(i-Pr)NH were added *via* a syringe. After acidic workup with citric acid and removal of the solvent, a solid was obtained that could be recrystallized to yield 4.87 g (49%) of **7**. M.p. 144–145°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40–7.15 (*m*, 10 arom. H); 5.64 (br. *d*, J = 9, 1 H–N(2)); 5.26 (br. *s*, 1 H–C(3)); 4.98 (*s*, PhCH_2OCON(2)); 4.59 (br. *d*, J = 9, 1 H–C(2)); 3.73 (*s*, Me); 2.91 (br. *s*, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.1 (*s*); 156.3 (*s*); 139.6 (*s*); 136.2 (*s*); 128.9 (*d*); 128.8 (*d*); 128.4 (*d*); 128.14 (*d*); 128.08 (*d*); 127.9 (*d*); 125.9 (*d*); 73.6 (*d*); 67.0 (*t*); 59.8 (*d*); 52.7 (*q*). EI-MS: 330 (1, $[M + 1]^+$), 270 (1), 223 (50), 126 (66), 107 (50), 91 (100), 77 (43), 65 (22).

*Methyl (2*R*,4*S*)- and (2*S*,4*S*)-3-[(Benzyloxy)carbonyl]-2-(*tert*-butyl)oxazolidine-4-carboxylate* (**8a** and **8b**). In 20 ml of benzene, 1.27 g (5.00 mmol) of Z-Ser-OMe (**3**), 2.20 ml (20.0 mmol) of *t*-BuCHO, 1.62 ml (7.50 mmol) of (i-PrO)$_3$CH, and 13 mg (1/500 equiv.) of **1** were dissolved. The colorless soln. was refluxed under Ar for

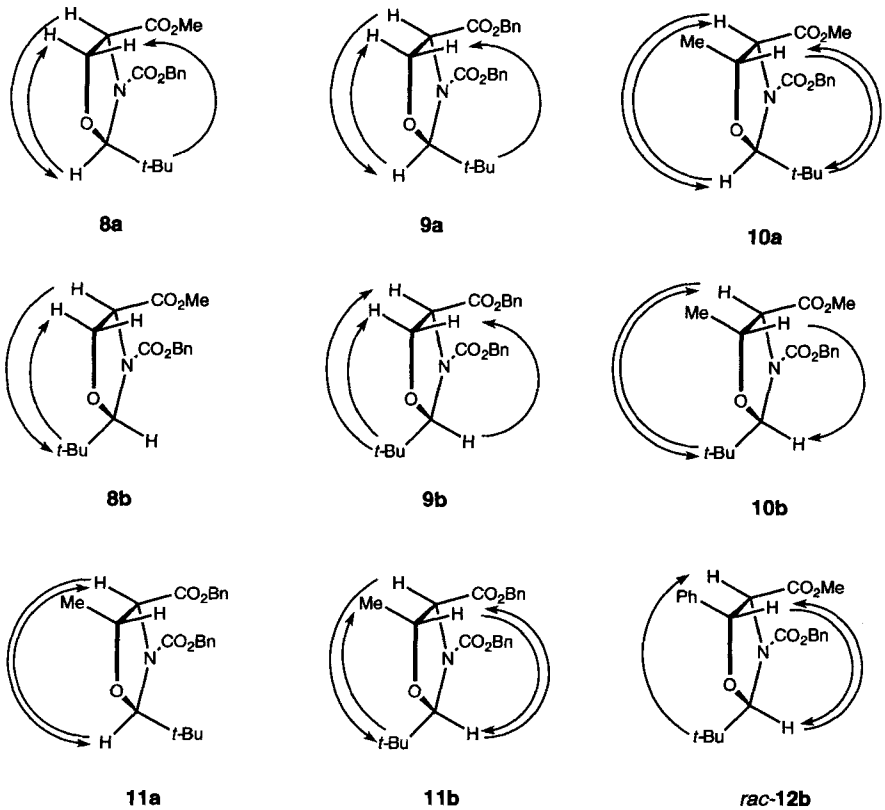

Fig. 1. *Nuclear* Overhauser *effects (NOEs) observed for oxazolidines* **8–12** *derived from Z-protected β-hydroxy-amino-acid esters* **3–7**

72 h. The orange-yellow soln. was evaporated to dryness under reduced pressure. The resulting residue was dissolved in pentane and filtered through a *Pasteur* pipette containing basic aluminum oxide. The filtrate was concentrated to dryness. The crude epimers were purified by FC (neat CH_2Cl_2): 1.12 g of the liquid *cis*- and 0.28 g of the solid *trans*-epimer were obtained (total yield of the *cis*- and *trans*-products: 87%). The latter was recrystallized from AcOEt and hexane.

Data of **8a**: $[\alpha]_D^{r.t.} = -18.1$ ($c = 1.34$, MeOH). R_f (CH_2Cl_2) 0.25. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.28 (*m*, 5 arom. H); 5.18 (*AB*, $J = 12$, PhCH_2); 5.09 (*s*, H–C(2)); 4.77 (br. *dd*, $J = 8$, 5, H–C(4)); 4.34 (*dd*, $J = 9$, 5, H–C(5)); 4.11 (*dd*, $J = 9$, 8, H–C(5)); 3.75 (*s*, Me); 0.93 (*s*, *t*-Bu). For NOEs observed for **8–12**, see *Fig. 1*. ^{13}C-NMR (100 MHz, $CDCl_3$): 170.6 (*s*); 155.9 (*s*); 135.9 (*s*); 128.3 (*d*); 128.2 (*d*); 128.0 (*d*); 97.7 (*d*); 68.3 (*t*); 67.9 (*t*); 59.7 (*d*); 52.4 (*q*); 37.6 (*s*); 25.7 (*q*). EI-MS: 320 (0.04, $[M - 1]^+$), 276 (0.1), 264 (35), 220 (55), 91 (100), 28 (20).

Data of **8b**: m.p. 87–88°. $[\alpha]_D^{r.t.} = -74.2$ ($c = 1.0$, MeOH). R_f (CH_2Cl_2) 0.17. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H); 5.26 (*s*, H–C(2)); 5.20–5.00 (*m*, PhCH_2); 4.45 (*dd*, $J = 7$, 2, H–C(4)); 4.37 (*dd*, $J = 9$, 7, H–C(5)); 4.04 (*dd*, $J = 9$, 2, H–C(5)); 3.48 (br. *s*, Me); 0.96 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.6 (*s*); 155.0 (*s*); 135.8 (*s*); 128.6 (*d*); 128.5 (*d*); 128.3 (*d*); 97.3 (*d*); 70.6 (*t*); 67.6 (*t*); 60.4 (*d*); 52.4 (*q*); 39.1 (*s*); 26.0 (*q*). EI-MS: 368 (2), 322 (1, $[M + 1]^+$), 276 (2), 264 (64), 220 (74), 130 (5), 91 (100), 57 (35).

*Benzyl (2*R*,4*S*)- and (2*S*,4*S*)-3-[(Benzyloxy)carbonyl]-2-(*tert*-butyl)oxazolidine-4-carboxylate* (**9a** and **9b**). In 20 ml of benzene, 1.66 g (5.04 mmol) of Z-Ser-OBn (**4**), 2.20 ml (20.0 mmol) of *t*-BuCHO, 1.62 ml (7.50 mmol) of (i-PrO)$_3$CH, and 13 mg (1/500 equiv.) of **1** were dissolved and refluxed under Ar for 24 h. GC showed an epimeric mixture at a *cis*/*trans* ratio of 19:81. After refluxing the mixture for another 48 h, the yellow soln. was evaporated to dryness under reduced pressure. The resulting sticky oil was dissolved in CH_2Cl_2/ pentane 1:10 and filtered through a *Pasteur* pipette containing basic aluminum oxide. The filtrate was concentrated to dryness. The residue was purified by column chromatography (Et_2O/pentane 1:5): 0.58 g (27%) of the *cis*- and 0.69 g (35%) of the *trans*-product were isolated. If the entire reaction time was as long as 144 h, a *cis*/*trans* mixture of 76:24 was obtained. In this case, the yield slightly dropped to 53%.

Data of **9a**: $[\alpha]_D^{r.t.} = -16.1$ ($c = 1.0$, MeOH). R_f (Et_2O/pentane 1:4) 0.27. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.27 (*m*, 10 arom. H); 5.17 (*AB*, $J = 12$, PhCH_2O_2C); 5.15 (*s*, PhCH_2OCON(3)); 5.10 (*s*, H–C(2)); 4.79 (br. *dd*, $J = 8$, 5, H–C(4)); 4.32 (*dd*, $J = 9$, 5, H–C(5)); 4.14 (*dd*, $J = 9$, 8, H–C(5)); 0.90 (*s*, *t*-Bu). ^{13}C-NMR (125 MHz, $CDCl_3$): 169.9 (*s*); 155.8 (*s*); 135.9 (*s*); 135.2 (*s*); 128.6 (*d*); 128.5 (*d*); 128.4 (*d*); 128.3 (*d*); 128.2 (*d*); 128.0 (*d*); 98.0 (*d*); 68.4 (*t*); 67.8 (*t*); 67.2 (*t*); 59.7 (*d*); 37.7 (*s*); 25.7 (*q*). EI-MS: 340 (14, $[M - 57]^+$), 296 (33), 91 (100), 65 (11).

Data of **9b**: $[\alpha]_D^{r.t.} = -60.1$ ($c = 1.2$, MeOH). R_f (Et_2O/pentane 1:4) 0.30. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35–7.20 (*m*, 10 arom. H); 5.28 (*s*, H–C(2)); 5.12–4.89 (*s*, *AB*, PhCH_2OCON(3), PhCH_2O_2C); 4.48 (*dd*, $J = 5$, 2, H–C(4)); 4.36 (*dd*, $J = 9$, 5, H–C(5)); 4.03 (*dd*, $J = 9$, 2, H–C(5)); 0.95 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.0 (*s*); 155.0 (*s*); 135.7 (*s*); 135.2 (*s*); 128.5 (*d*); 128.44 (*d*); 128.40 (*d*); 128.3 (*d*); 128.2 (*d*); 97.3 (*d*); 70.5 (*t*); 67.5 (*t*); 67.1 (*t*); 60.5 (*d*); 39.1 (*s*); 26.0 (*q*). EI-MS: 340 (18, $[M - 57]^+$), 296 (37), 91 (100), 65 (5), 28 (18).

*Methyl (2*R*,4*S*,5*R*)- and (2*S*,4*S*,5*R*)-3-[(Benzyloxy)carbonyl]-2-(*tert*-butyl)-5-methyloxazolidine-4-carboxylate* (**10a** and **10b**). In 20 ml of benzene, 1.34 g (5.00 mmol) Z-Thr-OMe (**5**), 2.20 ml (20.0 mmol) of *t*-BuCHO, 1.08 ml (5.00 mmol) of (i-PrO)$_3$CH and 15 mg (1/500 equiv.) of **1** were dissolved. The mixture was refluxed under Ar for 24 h. The colorless soln. was evaporated to dryness under reduced pressure. The epimeric mixture was separated by FC yielding 1.26 g (total yield: 75%) of a 9:91 mixture of the two epimers. If the soln. is refluxed for another 61 h, the ratio increased to 25:75. The yield then dropped to 60%.

Data of **10a**: $[\alpha]_D^{r.t.} = -10.1$ ($c = 1.0$, MeOH). R_f (CH_2Cl_2) 0.40. IR ($CHCl_3$): 3020*m*, 2980*m*, 1750*s*, 1720*s*, 1510*m*, 1412*m*, 1333*m*, 1200*m*, 1138*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H); 5.23 (*s*, H–C(2)); 5.07 (*AB*, $J = 12$, PhCH_2); 4.10 (*m*, $J = 8$, 6, H–C(5)); 3.77 (*d*, $J = 8$, H–C(4)); 3.51 (*s*, MeO$_2$C); 1.30 (*d*, $J = 6$, Me); 0.90 (*s*, *t*-Bu). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.5 (*s*); 155.8 (*s*); 136.1 (*s*); 128.5 (*d*); 128.2 (*d*); 127.9 (*d*); 97.7 (*d*); 77.7 (*d*); 67.8 (*d*); 66.5 (*d*); 52.3 (*q*); 38.1 (*s*); 25.8 (*q*); 17.5 (*q*). EI-MS: 336 (0.1, $[M + 1]^+$), 278 (27), 234 (40), 129 (6), 91 (100), 57 (3).

Data of **10b**: $[\alpha]_D^{r.t.} = -57.2$ ($c = 1.04$, MeOH). R_f (CH_2Cl_2) 0.37. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H); 5.29 (*s*, H–C(2)); 5.13 (*s*, PhCH_2); 4.52 (*m*, $J = 6$, H–C(5)); 4.18 (*d*, $J = 8$, H–C(4)); 3.72 (*s*, MeO$_2$C); 1.36 (*d*, $J = 6$, Me); 0.95 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.5 (*s*); 155.8 (*s*); 136.1 (*s*); 128.5 (*d*); 128.2 (*d*); 127.9 (*d*); 97.7 (*d*); 77.2 (*d*); 67.8 (*t*); 66.5 (*d*); 52.3 (*q*); 38.3 (*s*); 26.0 (*q*); 20.2 (*q*). EI-MS: 336 (0.1 $[M + 1]^+$), 278 (27), 234 (40), 129 (6), 91 (100), 57 (3).

*Benzyl (2*R*,4*S*,5*R*)- and (2*S*,4*S*,5*R*)-3-[(Benzyloxy)carbonyl]-2-(*tert*-butyl)-5-methyloxazolidine-4-carboxylate* (**11a** and **11b**). In 20 ml of benzene, 1.65 g (4.80 mmol) Z-Thr-OBn (**6**), 2.20 ml (20.0 mmol) of *t*-BuCHO, 1.62 ml (7.5 mmol) (i-PrO)$_3$CH, and 13 mg (1/480 equiv.) of **1** were suspended. The mixture was refluxed under Ar for 72 h. The soln. was evaporated to dryness under reduced pressure. The residue was dissolved in pentane and

filtered through a *Pasteur* pipette containing basic aluminum oxide. The colorless pentane filtrate was concentrated to dryness. The crude epimers were separated and purified by FC yielding 1.04 g (total yield: 87%) of a *cis/trans*-mixture (4:96). After an entire reaction time of 36 h, a 25:75 mixture was obtained in 57%.

Data of **11a**: $[\alpha]_D^{r.t.} = -14.3$ ($c = 1.0$, MeOH). R_f (Et_2O/pentane 1:5) 0.31. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40–7.20 (*m*, 10 arom. H); 5.20–5.00 (*m*, H–C(2), 2 PhCH_2); 4.51 (*dq*, $J = 7$, 6 H–C(5)); 4.21 (*d*, $J = 7$, H–C(4)); 1.37 (*d*, $J = 6$, Me); 0.94 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.2 (*s*); 151.6 (*s*); 135.3 (*s*); 128.6 (*d*); 128.5 (*d*); 128.43 (*d*); 128.39 (*d*); 128.2 (*d*); 128.1 (*d*); 97.8 (*d*); 74.3 (*d*); 67.1 (*t*); 66.5 (*d*); 65.8 (*d*); 38.3 (*s*); 28.3 (*q*); 26.0 (*q*). EI-MS: 368 (8), 354 (26), 324 (10), 310 (54), 91 (100), 57 (12).

Data of **11b**: $[\alpha]_D^{r.t.} = -18.1$ ($c = 1.34$, MeOH). R_f (Et_2O/pentane 1:5) 0.33. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.20 (*m*, 10 arom. H); 5.23 (*s*, H–C(2)); 4.99 (*AB*, $J = 12$, PhCH_2O_2C); 5.00 (br. *s*, PhCH_2OCON(3)); 4.11 (*dq*, $J = 9$, 6, H–C(5)); 3.82 (*d*, $J = 9$, H–C(4)); 1.27 (*d*, $J = 6$, Me); 0.91 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.6 (*s*); 153.5 (*s*); 135.7 (*s*); 135.2 (*s*); 128.6 (*d*); 128.53 (*d*); 128.48 (*d*); 128.4 (*d*); 128.31 (*d*); 128.3 (*d*); 96.8 (*d*); 77.8 (*d*); 67.4 (*t*); 67.2 (*t*); 66.3 (*d*); 37.9 (*s*); 25.6 (*q*); 17.4 (*q*). EI-MS: 410 (0.1, $[M - 1]^+$), 354 (7), 310 (17), 91 (100), 57 (11), 28 (14).

*Methyl (2*R**,4*R**,5*S**)-3-[(Benzyloxy)carbonyl]-2-(*tert*-butyl)-5-phenyloxazolidine-4-carboxylate* (**12b**). In 20 ml of benzene, 1.01 g (2.5 mmol) of *rac*-Z-PhSer-OBn (**7**), 1.10 ml (10.0 mmol) of *t*-BuCHO, 0.81 ml (3.75 mmol) of (i-PrO)$_3$CH, and 6.5 mg (1/500 equiv.) of **1** were dissolved. The soln. was refluxed under Ar for 76 h. The orange-yellow soln. was evaporated to dryness under reduced pressure. The resulting residue was purified by FC yielding 0.39 g (39%) of **12b**.

Data of **12b**: R_f (Et_2O/pentane) 0.35. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.28 (*m*, 10 arom. H); 5.39 (*s*, H–C(2)); 5.10 (*AB*, $J = 12$, PhCH_2); 5.02 (*d*, $J = 8$, H–C(5)); 4.01 (*d*, $J = 8$, H–C(4)); 3.48 (br. *s*, Me); 1.01 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.7 (*s*); 153.5 (*s*); 136.1 (*s*); 135.5 (*s*); 128.8 (*d*); 128.7 (*d*); 128.5 (*d*); 128.4 (*d*); 126.1 (*d*); 125.8 (*d*); 96.7 (*d*); 82.9 (*d*); 67.6 (*t*); 66.6 (*d*); 52.3 (*q*); 38.2 (*s*); 25.8 (*q*). FAB-MS: 398 (20, $[M + 1]^+$), 352 (14), 340 (58), 312 (52), 296 (25), 262 (13), 91 (100), 57 (19).

*Methyl (2*R,4*S,5*R)- and (2*S,4*S,5*R)-3-[(Benzyloxy)carbonyl]-2-isopropoxy-5-methyloxazolidine-4-carboxylate* (**13**). In 20 ml of benzene, 1.34 g (5.00 mmol) of Z-Thr-OMe (**5**), 1.08 ml (5.00 mmol) of (i-PrO)$_3$CH, and 15 mg (1/500 equiv.) of **1** were dissolved. The mixture was refluxed under Ar for 12 h. The soln. was evaporated to dryness under reduced pressure. The crude mixture was treated with pentane and filtrated through a *Pasteur* pipette containing cotton. Thus, a *ca.* 1:1 mixture of the epimers was obtained in 90% yield (1.46 g). The products could further be purified, but not separated, by FC without any problems. IR ($CHCl_3$): 3010*m*, 2980*m*, 1756*m*, 1717*s*, 1418*m*, 1349*m*, 1058*s*, 1011*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.20 (*m*, 5 arom. H); 6.14, 6.03 (2*s*, H–CN(2)); 5.30–4.90 (*m*, PhCH_2); 4.60–4.30 (*m*, H–C(3)); 4.25–3.80 (*m*, Me_2CH, H–C(2)); 3.78, 3.69 (2*s*, MeO_2C(1)); 1.50 (*d*, $J = 6$, 3 H–C(4), minor diastereoisomer); 1.42 (*d*, $J = 6$, 3 H–C(4), major diastereoisomer); 1.32–1.00 (*m*, Me_2CH). EI-MS: 295 (0.2, $[M - 42]^+$), 278 (20), 234 (27), 171 (4), 91 (100), 28 (34).

N^l-[(Isobutoxy)carbonyl]serylvaline Methyl Ester (^{i}BuOCO-Ser-Val-OMe, **14**). In 3 steps, **14** was synthesized by coupling Z-O-Bn-Ser-OH with H-Val-OMe according to the mixed-anhydride method [32], partial hydrogenolysis with Pd on charcoal, acylation with isobutyloxycarbonyl chloride of the resulting amine, and removal of the Bn protecting group again with Pd on charcoal. $[\alpha]_D^{r.t.} = -26.4$ ($c = 1.0$, MeOH). R_f (Et_2O) 0.19. ^{1}H-NMR (30 MHz, $CDCl_3$): 7.13 (br. *d*, $J = 8$, H–N(2.2)); 5.84 (*d*, $J = 7$, H–N(2.1)); 4.51 (*dd*, $J = 9$, 5, H–C(2.2)); 4.30 (br. *m*, H–C(2.1)); 4.06 (*dd*, $J = 11$, 3, H–C(3.1)); 3.87 (*ABX*, $J = 13$, 7, 7, i-PrCH_2OCON(2.1)); 3.75 (*s*, MeO_2C(1.2)); 3.68 (*dd*, $J = 11$, 5, H–C(3.1)); 3.53 (br. *s*, OH); 2.21 (*m*, $J = 7$, 5, 1 H–C(3.2)); 1.92 (*m*, $J = 7$, Me_2CHCH$_2$OCON(2.1)); 1.00–0.90 (4*d*, Me_2CHCH$_2$OCON(2.1), 3 H–C(4.2), 3 H–C(4′.2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.3 (*s*); 171.4 (*s*); 157.1 (*s*); 71.7 (*t*); 62.9 (*t*); 57.5 (*d*); 55.1 (*d*); 52.3 (*q*); 30.8 (*d*); 28.0 (*d*); 19.0 (*q*); 17.6 (*q*). FAB-MS: 341 (28, $[M + 1]^+$), 288 (7), 219 (11), 188 (9), 154 (11), 132 (50), 72 (50).

*N^l-[(*tert*-Butoxy)carbonyl]serylvaline Benzyl Ester* (Boc-Ser-Val-OBn, **15**). According to the mixed-anhydride methode [32], 2.05 g (10.0 mmol) of Boc-protected serine and 2.43 g (10.0 mmol) of valine benzyl ester hydrochloride were coupled yielding quantitatively the desired dipeptide. $[\alpha]_D^{r.t.} = -27.3$ ($c = 1.3$, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H); 7.15 (br. *d*, $J = 9$, H–N(2.2)); 5.18 (*AB*, $J = 9$, PhCH_2); 4.55 (*dd*, $J = 9$, 5, H–C(2.2)); 4.19 (*m*, H–C(2.1)); 4.07 (br. *d*, H–C(3.1)); 3.64 (*dd*, $J = 11$, 5, H–C(3.1)); 3.32 (br. *s*, OH); 2.22 (*m*, H–C(3.2)); 1.45 (*s*, *t*-Bu); 0.89 (*d*, $J = 7$, 3 H–C(4.2)); 0.86 (*d*, $J = 7$, 3 H–C(4′.2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.8 (*s*); 171.6 (*s*); 156.2 (*s*); 135.3 (*s*); 128.6 (*d*); 128.5 (*d*); 128.4 (*d*); 80.5 (*s*); 67.2 (*t*); 62.8 (*t*); 57.4 (*d*); 54.6 (*d*); 30.9 (*d*); 28.3 (*q*); 19.1 (*q*); 17.4 (*q*). FAB-MS: 417 (10, $[M + 23]^+$), 395 (13, $[M + 1]^+$), 339 (34), 295 (35), 91 (100), 72 (65), 57 (57).

N^l-[(Benzyloxy)carbonyl]serylvaline Methyl Ester (Z-Ser-Val-OMe, **16**). According to the mixed-anhydride method [32], 13.3 g (59.7 mmol) of Z-protected serine and 10.0 g (59.7 mmol) of valine benzyl ester hydrochloride were coupled yielding quantitatively the desired dipeptide. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H);

6.92 (br. *d*, *J* = 6, 1 H–N(2.2)); 5.82 (br. *d*, *J* = 6, 1 H–N(2.1)); 5.14 (*AB*, *J* = 11, PhCH_2); 4.50 (*d*, *J* = 9, 5, H–C(2.2)); 4.27 (*m*, 1 H–C(2.1)); 4.10 (*dd*, *J* = 11, 2, H–C(3.1)); 3.75 (*s*, Me); 3.66 (*dd*, *J* = 11, 6, H–C(3.1)); 2.17 (*m*, H–C(3.2)); 2.09 (br. *s*, OH); 0.91 (*d*, *J* = 7, 3 H–C(4.2)); 0.87 (*d*, *J* = 7, 3 H–C(4′.2)).

N^{l}-*[(Benzyloxy)carbonyl]serylphenylalanine Ethyl Ester* (Z-Ser-Phe-OEt, **17**). This dipeptide was synthesized in two steps by first coupling Z-O-TBS-Ser-OH and the hydrochloride of H-Phe-OEt according to the mixed-anhydride method [32]. Then, the silyl protecting group was removed by 2.0 equiv. of Bu_4NF in CH_2Cl_2. $[\alpha]_D^{r.t.} = -31.1$ (*c* = 1.1, MeOH). R_f (AcOEt) 0.46. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.05 (*m*, 10 arom. H); 6.90 (br. *d*, *J* = 8, H–N(2.2)); 6.72 (br. *d*, *J* = 8, H–N(2.1)); 5.10 (*s*, PhCH_2OCON(2.1)); 4.71 (*q*, *J* = 7, H–C(2.2)); 4.14 (*q*, *J* = 7, CH_2O_2C(1.2)); 3.98 (*m*, H–C(3.1)); 3.60 (*m*, H–C(3.1)); 3.10 (*m*, 2 H–C(3.2)); 1.75 (br. *s*, OH); 1.24 (*t*, *J* = 7, Me).

N^{l}-*[(Benzyloxy)carbonyl]threonylglycine Benzyl Ester* (Z-Thr-Gly-OBn, **18**). According to the mixed-anhydride method, 1.50 g (5.92 mmol) of Z-protected threonine and 2.99 g (8.88 mmol) of glycine benzyl ester hydrotosylate were coupled: 2.11 g (89%) of **18** was obtained that was further purified by recrystallization from AcOEt/hexane. Mp. 102–102.5°. $[\alpha]_D^{r.t.} = -14.4$ (*c* = 0.9, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.27 (*m*, 10 arom. H); 7.12 (br. *t*, *J* = 5, 2 H–C(2.2)); 5.89 (br. *d*, *J* = 8, H–N(2.1)); 5.15 (*s*, PhCH_2OCON(2.1)); 5.11 (*s*, PhCH_2O_2C(1.2)); 4.36 (*m*, H–C(3.1)); 4.21 (*dd*, *J* = 8, 6, H–C(2.1)); 4.04 (*ABX*, *J* = 14, 6, 4, 2 H–C(2.2)); 3.40 (br. *s*, OH); 1.18 (*d*, *J* = 6, 3 H–C(4.1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.5 (*s*); 169.7 (*s*); 156.9 (*s*); 136.1 (*s*); 135.1 (*s*); 128.7 (*d*); 128.6 (*d*); 128.4 (*d*); 128.3 (*d*); 128.0 (*d*); 67.4 (*t*); 67.1 (*d*); 58.9 (*d*); 41.4 (*t*); 18.2 (*q*). FAB-MS: 801 (4, $[2M + 1]^+$), 423 (12, $[M + 23]^+$), 401 (40, $[M + 1]^+$), 357 (22), 181 (12), 137 (16), 91 (100).

N^{l}-*[(Benzyloxy)carbonyl]threonylphenylalanine* tert-*Butyl Ester* (Z-Thr-Phe-O^{t}Bu, **19**). According to the mixed-anhydride method [32], 6.41 g (25.3 mmol) of Z-Thr-OH and 6.75 g (27.4 mmol) of the hydrochloride of H-Phe-O^{t}Bu were coupled quantitatively to dipeptide **19**. $[\alpha]_D^{r.t.} = -63.8$ (*c* = 1.1, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.10 (*m*, 10 arom. H); 6.91 (br. *d*, *J* = 3, 1 H–N(2.2)); 5.67 (br. *d*, *J* = 8, 1 H–N(2.1)); 5.11 (*s*, PhCH_2); 4.75 (*q*, 1 H–C(2.2)); 4.30 (*m*, 1 H–C(3.1)); 4.12 (*dd*, *J* = 9, 2, 1 H–C(2.1)); 3.01 (*m*, 2 H–C(3.2)); 1.73 (br. *s*, OH); 1.42 (*s*, *t*-Bu); 1.14 (*d*, *J* = 7, 3 H–C(4.1)). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.9 (*s*); 170.7 (*s*); 157.1 (*s*); 136.3 (*s*); 129.7 (*d*); 128.9 (*d*); 128.8 (*d*); 128.6 (*d*); 128.4 (*d*); 127.4 (*d*); 82.9 (*s*); 67.5 (*t*); 67.1 (*d*); 58.6 (*d*); 53.9 (*d*); 38.1 (*t*); 28.2 (*q*); 18.3 (*q*).

Isobutyl (2R,4S)- and (2S,4S)2-Isopropyl-4-{N-*[(S)-1-(methoxycarbonyl)-2-methylpropyl]carbamoyl*}*-oxazolidine-3-carboxylate* (**20′** and **20″**). In a 100-ml flask, 1.59 g (5.00 mmol) of ^{i}BuOCO-Ser-Val-OMe (**14**), 1.80 ml (8.30 mmol) of (i-PrO)$_3$CH, 2.28 ml (25 mmol) of i-PrCHO, and 20 mg (1/500 equiv.) of **1** were heated to reflux in 50 ml of benzene for 50 h. The solvent was removed at reduced pressure and the residual mixture dried at high vacuum. FC of the mixture yielded 278 mg (15%) of one liquid and 237 mg (13%) of one solid epimer.

Data of **20′**: $[\alpha]_D^{r.t.} = -39.1$ (*c* = 1.4, MeOH). R_f (Et_2O/pentane 1:1) 0.24. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.25 (br. *s*, NH); 4.98 (*d*, *J* = 6, H–C(2)); 4.60–4.40 (*m*, H–C(5), H–C(4), CHCO$_2$Me); 4.15–3.80 (*m*, H–C(5), ^{i}PrCH_2); 3.73 (*s*, MeO$_2$C); 2.25–2.03 (*m*, CHCHCO$_2$Me, Me$_2$CHCH$_2$OCON(3)); 1.94 (*m*, *J* = 9, Me$_2$CHC(2)); 1.00–0.86 (6*d*, *Me*$_2$CHCH$_2$, *Me*$_2$CHC(2), *Me*$_2$CHCHCO$_2$Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.6; 169.8; 155.8; 94.7; 72.2; 66.9; 59.2; 57.0; 51.8; 31.0; 30.6; 27.6; 18.71; 18.65; 18.0; 17.4; 15.8. FAB-MS: 373 (100, $[M + 1]^+$), 329 (71), 319 (46), 245 (48), 185 (46), 115 (52), 73 (68). Anal. calc. for $C_{18}H_{32}N_2O_6$: C 58.05, H 8.66, N 7.52, O 25.77; found: C 58.28, H 8.46, N 7.46.

Data of **20″**: $[\alpha]_D^{r.t.} = -96.8$ (*c* = 0.8, MeOH). R_f (Et_2O/pentane 1:1) 0.18. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.37 (br. *s*, NH); 5.20 (*d*, *J* = 3, H–C(2)); 4.51 (*dd*, *J* = 9, 5, CHCO$_2$Me); 4.38 (*dd*, *J* = 7, 3, H–C(4)); 4.23 (*t*, *J* = 9, H–C(5)); 4.08 (*dd*, *J* = 9, 3, H–C(5)); 3.95–3.75 (*m*, ^{i}PrCH_2); 3.70 (*s*, MeO$_2$C); 2.38 (*m*, Me$_2$CHC(2)); 2.13 (*m*, CHCHCO$_2$Me); 1.88 (*m*, *J* = 7, Me$_2$CHCH$_2$); 1.00–0.81 (6*d*, Me$_2$CHCH$_2$, *Me*$_2$CHC(2), *Me*$_2$CHCHCO$_2$Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.5 (*s*); 170.8 (*s*); 153.8 (*s*); 94.5 (*d*); 72.2 (*t*); 70.5 (*t*); 60.5 (*d*); 57.3 (*d*); 52.4 (*q*); 31.6 (*d*); 31.5 (*d*); 28.1 (*d*); 19.2 (*q*); 19.1 (*q*); 18.5 (*q*); 17.9 (*q*); 15.4 (*q*). FAB-MS: 745 (3, $[2M + 1]^+$), 701 (6), 373 (98, $[M + 1]^+$), 329 (100), 271 (16), 245 (47), 229 (38), 185 (44), 169 (36), 114 (28). Anal. calc. for $C_{18}H_{32}N_2O_6$: C 58.05, H 8.66, N 7.52, O 25.77; found: C 58.22, H 8.48, N 7.48.

*Isobutyl (2S,4S)-2-(*tert-*Butyl)-4-*{N-*[(S)-1-(methoxycarbonyl)-2-methylpropyl]carbamoyl*}*oxazolidine-3-carboxylate* (**21b**). In 20 ml of benzene, 1.59 g (5.01 mmol) ^{i}BuOCO-Ser-Val-OMe (**14**), 2.25 ml (20.5 mmol) of *t*-BuCHO, 1.62 ml (7.50 mmol) of (i-PrO)$_3$CH, and 26 mg (1/250 equiv.) of **1** were dissolved, resulting in an orange soln. The soln. was refluxed under Ar for 20 h. Half of the orange-yellow soln. was evaporated to dryness under reduced pressure. The resulting residue was purified by FC yielding 1.49 g (77%) of **21b**.

Data of **21b**: $[\alpha]_D^{r.t.} = -47.5$ (*c* = 1.2, MeOH). R_f (Et_2O/pentane 1:2) 0.19. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43 (br. *d*, NH); 5.15 (*s*, H–C(2)); 4.61 (*m*, 2 H–C(5)); 4.48 (*dd*, *J* = 8, 5, CHCO$_2$Me); 4.13 (*t*, *J* = 8, H–C(4)); 4.00 (*d*, *J* = 7, ^{i}PrCH_2); 3.75 (*s*, MeO$_2$C); 2.19 (*m*, *J* = 7, 5, Me$_2$CHCHCO$_2$Me); 1.99 (*m*, *J* = 7, *Me*$_2$CHCH$_2$OCON(3)); 1.00–0.90 (4*d*, *Me*CHCH$_2$, *Me*$_2$CHCHCO$_2$Me); 0.93 (*s*, *t*-Bu). For NOEs observed for **21**–**26**, see *Fig. 2*. ^{13}C-NMR

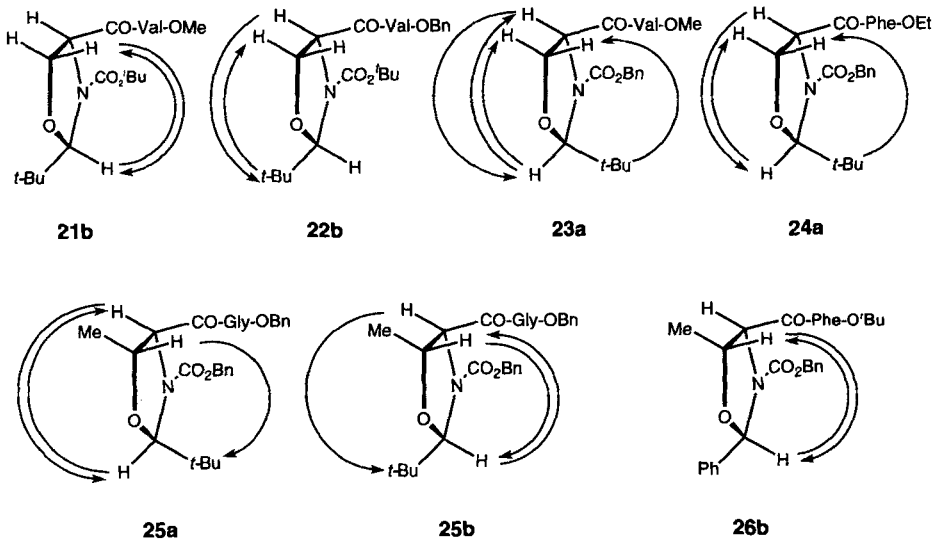

Fig. 2. *Nuclear* Overhauser *effects (NOEs) observed for oxazolidine containing dipeptides* **21–26** *derived from urethane-protected dipeptides* **14–19** *containing serine or threonine*

(100 MHz, $CDCl_3$): 172.0 (*s*); 170.0 (*s*); 157.6 (*s*); 97.8 (*d*); 73.0 (*t*); 67.6 (*t*); 60.6 (*d*); 57.6 (*d*); 52.2 (*q*); 37.4 (*s*); 31.0 (*d*); 27.9 (*d*); 25.8 (*q*); 19.1 (*q*); 19.0 (*q*); 17.9 (*q*). FAB-MS: 387 (75, $[M + 1]^+$), 329 (100), 285 (12), 245 (53), 229 (34), 185 (49), 169 (31), 72 (33), 57 (84).

tert-*Butyl (2*R,*4*S*)- and (2*S,*4*S*)-4-*{N-*{*(S)*-*1-[(Benzyloxy)carbonyl]-2-methylpropyl}carbamoyl}-2-*tert-*butyloxazolidine-3-carboxylate* (**22a** and **22b**). In 20 ml of benzene, 1.97 g (5.00 mmol) of Boc-Ser-Val-OBn (**15**), 1.65 ml (15.0 mmol) of *t*-BuCHO, 1.62 ml (7.5 mmol) of $(i\text{-PrO})_3CH$, and 13 mg (1/500 equiv.) of **1** were dissolved. The orange soln. was refluxed under Ar for 12 h. The orange-yellow soln. was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered through a *Pasteur* pipette containing basic aluminum oxide. The filtrate was evaporated to dryness. The resulting oil was purified by FC. Thus, 0.18 g (8%) of the *cis*-epimer **22a** and 1.46 g (63%) of the *trans*-epimer **22b** were obtained.

Data of **22a**: $[\alpha]_D^{rt} = -58.7$ ($c = 0.69$, MeOH). R_f (Et_2O/pentane 1:1) 0.28. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.65 (br. *d*, NH); 7.40–7.30 (*m*, 5 arom. H); 5.18 (*AB*, $J = 12$, $PhCH_2$); 5.10 (*s*, H–C(2)); 4.65–4.49 (*m*, H–C(5), H–C(4)); 4.13 (*m*, H–C(5)); 2.22 (*m*, $CHCHCO_2Bn$); 1.51 (*s*, *t*-Bu); 0.98 (*d*, $J = 7$, $MeCHCHCO_2Bn$); 0.92 (*d*, $J = 7$, $MeCHCHCO_2Bn$); 0.90 (*s*, *t*-Bu–C(2)). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4 (*s*); 170.4 (*s*); 156.5 (*s*); 135.5 (*s*); 128.6 (*d*); 128.3 (*d*); 97.6 (*d*); 82.5 (*s*); 67.5 (*t*); 66.9 (*t*); 60.2 (*d*); 57.5 (*d*); 37.5 (*s*); 31.0 (*d*); 28.1 (*q*); 25.9 (*q*); 19.1 (*q*); 17.6 (*q*). FAB-MS: 925 (5, $[M + 1]^+$), 867 (4), 463 (44), 405 (19), 363 (84), 305 (86), 154 (17), 129 (69), 91 (100). Anal. calc. for $C_{25}H_{38}N_2O_6$: C 64.91, H 8.28, N 6.06, O 20.75; found: C 65.12, H 8.26, N 5.99.

Data of **22b**: $[\alpha]_D^{rt} = -97.0$ ($c = 0.62$, MeOH). R_f (Et_2O/pentane 1:1) 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H); 6.06 (br. *s*, NH); 5.25 (*s*, H–C(2)); 5.15 (*m*, $J = 12$, $PhCH_2$); 4.59 (br. *s*, $CHCO_2Bn$); 4.35 (*dd*, $J = 9, 7$, H–C(5)); 4.26 (*dd*, $J = 7, 2$, H–C(4)); 4.02 (*dd*, $J = 9, 2$, 1 H–C(5)); 2.19 (*m*, $CHCHCO_2Bn$); 1.41 (*s*, *t*-Bu); 0.97 (*s*, *t*-Bu–C(2)); 0.94 (*d*, $J = 7$, $MeCHCHCO_2Bn$); 0.88 (*d*, $J = 7$, $MeCHCHCO_2Bn$). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.5 (*s*); 171.2 (*s*); 153.7 (*s*); 135.3 (*s*); 128.6 (*d*); 128.5 (*d*); 96.7 (*d*); 81.2 (*s*); 71.1 (*d*); 67.1 (*d*); 60.0 (*t*); 57.2 (*t*); 39.3 (*s*); 31.7 (*d*); 28.1 (*q*); 26.4 (*q*); 18.9 (*q*); 17.8 (*q*). FAB-MS: 925 (7, $[2M + 1]^+$), 867 (7), 463 (44, $[M + 1]^+$), 405 (17), 363 (82), 305 (96), 154 (39), 91 (100). Anal. calc. for $C_{25}H_{38}N_2O_6$: C 64.91, H 8.28, N 6.06, O 20.75; found: C 64.68, H 7.86, N 6.04.

*Benzyl (2*R,*4*S*)-2-(*tert-*Butyl)-4-*{N-*[(*S*)-*1-(methoxycarbonyl)-2-methylpropyl]carbamoyl}oxazolidine-3-carboxylate* (**23a**). In 20 ml of benzene, 1.76 g (5.00 mmol) of Z-Ser-Val-OMe (**16**), 1.70 ml (15.0 mmol) of *t*-BuCHO, 1.62 ml (7.50 mmol) of $(i\text{-PrO})_3CH$, and 13 mg (1/500 equiv.) of **1** were dissolved. The soln. was refluxed under Ar for 21 h. The orange-yellow soln. was evaporated under reduced pressure to dryness. The resulting residue was purified by FC yielding 1.63 g (78%) of **23a**.

Data of **23a**: $[\alpha]_D^{r.t.} = -37.9$ ($c = 0.9$, MeOH). R_f (CH_2Cl_2/Et_2O 9:1) 0.31. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.31 (*m*, 5 arom. H); 5.24 (*m*, $J = 12$, PhCH_2); 5.15 (*s*, H–C(2)); 4.65 (*dd*, $J = 8, 5$, H–C(5)); 4.59 (*dd*, $J = 8, 5$, H–C(5)); 4.44 (*dd*, $J = 8, 5$, CHCO$_2$Me); 4.10 (*t*, $J = 8$, H–C(4)); 3.72 (*s*, MeO$_2$C); 2.15 (*m*, CHCHCO$_2$Me); 0.89 (*s*, *t*-Bu–C(2)); 0.90 (*d*, $J = 7$, *Me*CHCHCO$_2$Me); 0.87 (*d*, $J = 7$, *Me*CHCHCO$_2$Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.9 (*s*); 169.9 (*s*); 157.2 (*s*); 135.5 (*s*); 128.6 (*d*); 128.5 (*d*); 97.9 (*d*); 68.5 (*t*); 67.6 (*t*); 60.6 (*d*), 57.7 (*d*); 52.1 (*q*); 37.4 (*s*); 30.9 (*d*); 25.8 (*q*); 19.0 (*q*); 17.8 (*q*). FAB-MS: 841 (1), 783 (82), 421 (51, $[M + 1]^+$), 363 (24), 319 (39), 91 (100).

*Benzyl (2*R*,4*S*)-2-(*tert*-Butyl)-4-{*N*-[(*S*)-[(ethoxycarbonyl)-2-phenylethyl]carbamoyl}oxazolidine-3-carboxylate* (**24a**). In 15 ml of benzene, 0.50 g (1.20 mmol) of Z-Ser-Phe-OEt (**17**), 0.39 ml (3.60 mmol) of *t*-BuCHO; 0.45 ml (2.08 mmol) of (i-PrO)$_3$CH, and 20 mg (1/100 equiv.) of **1** were heated to reflux. After 24 h, the solvent was removed under reduced pressure and the residue dried at high vacuum. The product was purified by FC: 216 mg (37%) of **24a** were obtained.

Data of **24a**: $[\alpha]_D^{r.t.} = -27.7$ ($c = 0.86$, MeOH). R_f (Et_2O/pentane 1:1) 0.24. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 arom. H of Z-group); 7.25–7.05 (*m*, 5 arom. H of Phe, NH); 5.15 (*s*, PhCH_2OCON(3)); 5.05 (*s*, H–C(2)); 4.71 (*td*, $J = 8, 6$, CHCO$_2$Et); 4.56 (*m*, 2 H–C(5)); 4.17 (*q*, $J = 7$, MeCH_2O$_2$C); 4.01 (*t*, $J = 8$, H–C(4)); 3.04 (*ABX*, $J = 14, 8, 6$, PhCH_2CH); 1.23 (*t*, $J = 7$, *Me*CH$_2$O$_2$C); 0.72 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3 (*s*); 169.5 (*s*); 156.8 (*s*); 136.1 (*s*); 135.5 (*s*); 129.4 (*d*); 129.1 (*d*); 128.6 (*d*); 128.4 (*d*); 127.1 (*d*); 97.8 (*d*); 68.4 (*t*); 67.3 (*t*); 61.4 (*t*); 60.5 (*d*); 53.8 (*d*); 37.9 (*t*); 37.2 (*s*); 25.6 (*q*); 14.1 (*q*). FAB-MS: 483 (23, $[M + 1]^+$), 425 (11), 397 (8), 381 (28), 120 (15), 91 (100), 77 (7).

*Benzyl (2*R*,4*S*,5*R*)- and (2*S*,4*S*,5*R*)-4-{*N*-[(*S*)-1-[(Benzyloxy)carbonyl]methyl}carbamoyl}-2-(*tert*-butyl)-5-methyloxazolidine-3-carboxylate* (**25a** and **25b**). In 45 ml of benzene, 1.52 g (3.82 mmol) of Z-Thr-Gly-OBn (**18**), 1.24 ml (11.5 mmol) of *t*-BuCHO, 1.40 ml (6.48 mmol) of (i-PrO)$_3$CH, and 10 mg (1/500 equiv.) of **1** were refluxed for 24 h. The solvent was evaporated and the epimeric mixture chromatographically separated. Thus, 1.17 g (65%) of **25a** and 0.25 g (15%) of **25b** were obtained.

Data of **25a**: $[\alpha]_D^{r.t.} = -22.5$ ($c = 1.1$, MeOH). R_f (Et_2O/pentane 2:1) 0.50. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.40–7.27 (*m*, 10 arom. H); 7.19 (br. *s*, NH); 5.20 (*s*, H–C(2)); 5.18 (*AB*, $J = 14$, PhCH_2OCON(3)); 5.18 (*AB*, $J = 12$, PhCH_2O$_2$CCH$_2$); 4.74 (*m*, $J = 6$, H–C(5)); 4.10 (*d*, $J = 6$, H–C(4)); 4.06 (*ABX*, $J = 18, 6, 5$, CH_2CO$_2$Bn); 1.36 (*d*, $J = 6$, Me–C(5)); 0.91 (*s*, *t*-Bu). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.7 (*s*); 169.2 (*s*); 157.2 (*s*); 135.4 (*s*); 135.1 (*s*); 128.7 (*d*); 128.58 (*d*); 128.5 (*d*); 128.4 (*d*); 128.3 (*d*); 97.6 (*d*); 76 (*d*); 68.4 (*t*); 67.2 (*t*); 67.1 (*d*); 41.3 (*t*); 37.7 (*s*); 26.0 (*q*); 20.6 (*q*). FAB-MS: 937 (1, $[2M + 1]^+$), 469 (41, $[M + 1]^+$), 411 (20), 367 (37), 339 (6), 181 (13), 91 (100). Anal. calc. for $C_{26}H_{32}N_2O_6$: C 66.65, H 6.88, N 5.98, O 20.49; found: C 66.57, H 6.81, N 5.80.

Data of **25b**: $[\alpha]_D^{r.t.} = -32.4$ ($c = 1.4$, MeOH). R_f (Et_2O/pentane 2:1) 0.48. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.42–7.30 (*m*, *Ph*CH$_2$OCON(3)); 7.35–7.20 (*m*, *Ph*CH$_2$O$_2$CCH$_2$); 6.34 (br. *t*, NH); 5.24 (*s*, H–C(2)); 4.13 (*dq*, $J = 8, 6$, H–C(5)); 4.00 (br. *s*, CHCO$_2$Bn); 3.56 (*d*, $J = 8$, H–C(4)); 3.53 (br. *s*, CHCO$_2$Bn); 1.39 (*d*, $J = 6$, Me–C(5)); 0.91 (*s*, *t*-Bu). ^{13}C-NMR (500 MHz, $CDCl_3$): 169.4 (*s*); 167.8 (*s*); 153.8 (*s*); 135.7 (*s*); 134.9 (*s*); 128.7 (*d*); 128.5 (*d*); 128.4 (*d*); 128.2 (*d*); 96.8 (*d*); 78.1 (*d*); 67.8 (*d*); 67.4 (*t*); 67.3 (*t*); 41.4 (*t*); 38.0 (*s*); 25.6 (*q*); 17.2 (*q*). FAB-MS: 937 (3, $[2M + 1]^+$), 879 (4, $[2M - 57]^+$), 469 (45, $[M + 1]^+$), 411 (28), 367 (47), 181 (18), 107 (13), 91 (100). Anal. calc. for $C_{26}H_{32}N_2O_6$: C 66.65, H 6.88, N 5.98, O 20.49; found: C 66.46, H 6.70, N 5.83.

*Benzyl (2*S*,4*S*,5*R*)-4-{*N*-[(*S*)-1-[(*tert*-Butoxy)carbonyl]-2-phenylethyl}carbamoyl}-2-(*tert*-butyl)oxazolidine-3-carboxylate* (**26b**). In 50 ml benzene, 2.28 g (5.00 mmol) of Z-Thr-Phe-O^{t}Bu (**19**), 1.52 ml (15.0 mmol) of PhCHO, 1.80 ml (8.33 mmol) of (i-PrO)$_3$CH, and 13 mg (1/500 equiv.) of **1** were refluxed for 17 h. The solvent was removed at reduced pressure. After chromatographical purification of the mixture, 667 mg (1.20 mmol) of the *trans*-product **26b** was obtained.

Data of **26b**: m.p. 153°. $[\alpha]_D^{r.t.} = -37.3$ ($c = 0.9$, MeOH). R_f (Et_2O/pentane 1:1) 0.34. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.10 (*m*, 15 arom. H); 6.28 (br. *s*, NH); 6.00 (*s*, H–C(2)); 4.90 (*AB*, $J = 12$, PhCH_2OCON(3)); 4.81 (*q*, $J = 7$, CHCO$_2{}^t$Bu); 4.23 (*m*, $J = 7$, H–C(5)); 3.98 (*d*, $J = 8$, H–C(4)); 3.07 (br. *AB*, PhCH_2CH); 1.44 (*d*, $J = 6$, Me–C(5)); 1.39 (*s*, ^{t}BuO$_2$C). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.1 (*s*); 168.0 (*s*); 152.7 (*s*); 138.2 (*s*); 135.9 (*s*); 135.7 (*s*); 129.7 (*d*); 129.3 (*d*); 128.6 (*s*); 128.4 (*s*); 128.4 (*s*); 128.2 (*d*); 127.8 (*d*); 127.5 (*d*); 127.0 (*d*); 91.4 (*d*); 82.6 (*s*); 78.2 (*d*); 67.5 (*d*); 67.3 (*t*); 53.5 (*d*); 38.0 (*t*); 28.0 (*q*); 18.4 (*q*). FAB-MS: 1089 (6, $[2M + 1]^+$), 545 (19, $[M + 1]^+$), 489 (53), 445 (18), 383 (18), 339 (9), 154 (21), 91 (100). Anal. calc. for $C_{32}H_{36}N_2O_6$: C 70.57, H 6.66, N 5.14, O 17.63; found: C 70.30, H 6.74, N 5.11.

N^1-Neopentylserylvaline Methyl Ester (**27**). In 50 ml of MeOH, 339 mg (0.81 mmol) of **23a** was treated with 100 mg of Pd on charcoal under H_2 at r.t. for 24 h. The mixture is filtrated through *Celite* and the solvent evaporated to dryness: 217 mg (94%) of the pure amine was isolated that could be further purified by chromatography.

Data of **27**: R_f (Et_2O/pentane 3:1) 0.12. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.91 (br. *d*, *J* = 10, H–N(2.2)); 4.50 (*dd*, *J* = 9, 5, H–C(2.2)); 3.81 (*m*, H–C(2.1)); 3.72 (*s*, *Me*O); 3.61 (br. *s*, OH or H–N(2.1)); 3.17 (*t*, *J* = 6, H–C(3.1)); 2.87 (*t*, *J* = 6, H–C(3.1)); 2.39 (*AB*, *J* = 11, ^{t}BuCH_2N(2.1)); 2.19 (*m*, H–C(3.2)); 1.65 (br. *s*, OH or H–N(2.1)); 0.96 (*d*, *J* = 7, 3 H–C(4.2)); 0.96 (*s*, ^{t}BuO_2C(1.2)); 0.89 (*d*, *J* = 7, 3 H–C(4′.2)). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.8; 171.7; 64.6; 62.8; 60.7; 56.4; 51.8; 31.3; 30.7; 27.3; 18.8; 17.3. FAB-MS: 577 (6, [2*M* + 1]$^+$), 545 (21, [2*M* − 31]$^+$), 311 (15, [*M* + 23]$^+$), 257 (8), 229 (7), 130 (47), 60 (17).

N^1-*[(*tert*-Butoxy)carbonyl]phenylalanyl*-N^2-*neopentylserylvaline Methyl Ester* (**28**). According to the method used in [47] for the coupling of hindered peptides with **33**, to a soln. of 95 mg (0.33 mmol) of **27**, 266 mg (1.00 mmol) of Boc-Phe-OH, and 522 mg (1.00 mmol) of **33** in 5 ml of CH_2Cl_2 were added 0.34 ml (2.01 mmol) of Et(i-Pr)$_2$N at −15°. The mixture was allowed to warm up to r.t. overnight and worked up with citric acid, aq. $NaHCO_3$, and aq. NaCl. After drying ($MgSO_4$), the solvent was removed at reduced pressure. Thus, 506 mg resulted that were further purified by FC yielding 90 mg (58%) of **28**.

Data of **28**: $[\alpha]_D^{r.t.} = -8.4$ (*c* = 0.16, MeOH). R_f (Et_2O/pentane 1:1) 0.16. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.91 (br. *d*, *J* = 9, H–N(2.3)); 7.35–7.10 (*m*, 5 arom. H); 5.02 (br. *d*, *J* = 8, H–N(2.1)); 4.54 (*m*, *J* = 7, H–C(2.1)); 4.52 (*dd*, *J* = 9, 5, H–C(2.3)); 4.42 (*dd*, *J* = 11, 4, H–C(2.2)); 4.29 (*dd*, *J* = 11, 7, H–C(3.2)); 3.73 (*s*, *Me*O_2C(1.3)); 3.26 (*dd*, *J* = 7, 4, H–C(3.2)); 3.06 (*d*, *J* = 6, 2 H–C(3.1)); 2.35 (*AB*, *J* = 11, 2 H–CN(2.2)); 2.19 (*m*, H–C(3.3)); 1.41 (*s*, ^{t}BuOCON(2.1), OH); 0.94 (*s*, *t*-Bu); 0.93 (*d*, *J* = 7, 3 H–C(4.3)); 0.80 (*d*, *J* = 7, 3 H–C(4′.3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.1 (*s*); 172.0 (*s*); 170.9 (*s*); 155.0 (*s*); 135.9 (*s*); 129.2 (*d*); 128.7 (*d*); 127.2 (*d*); 80.1 (*s*); 65.6 (*t*); 62.8 (*d*); 60.9 (*t*); 56.8 (*d*); 54.7 (*d*); 52.0 (*q*); 38.5 (*t*); 31.5 (*s*); 3.10 (*d*); 28.3 (*q*); 27.5 (*q*); 19.1 (*q*); 17.7 (*q*). FAB-MS: 1071 (6, [2*M* + 1]$^+$), 536 (100, [*M* + 1]$^+$), 480 (28), 377 (25), 321 (22), 271 (13), 154 (9), 120 (18), 91 (5). Anal. calc. for $C_{28}H_{43}N_3O_7$: C 63.02, H 8.12, N 7.87, O 20.99; found: C 63.25, H 8.19, N 7.99.

N^1-*[(Benzyloxy)carbonyl]alanyl*-N^2-*neopentylserylvaline Methyl Ester* (**29**). According to the method in [47] for the coupling of hindered peptides with **34**, to a soln. of 124 mg (0.44 mmol) of **27**, 291 mg (1.30 mmol) of Z-Ala-OH, and 495 mg (1.30 mmol) of **34** in 5 ml of DMF were added 0.29 ml (2.61 mmol) of *N*-methylmorpholine at −15°. The mixture was allowed to warm up to r.t. overnight; 50 ml of CH_2Cl_2 were added, and the soln. worked up with citric acid, aq. $NaHCO_3$, and aq. NaCl. After drying ($MgSO_4$), the solvent was removed at reduced pressure. Thus, 233 mg resulted that were further purified by FC yielding 192 mg (91%) of **29**.

Data of **29**: $[\alpha]_D^{r.t.} = -36.2$ (*c* = 0.9, MeOH). R_f (Et_2O/pentane 3:1) 0.37. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.90 (br. *d*, *J* = 9, 1 H–N(2.3)); 7.40–7.27 (*m*, 5 arom. H); 5.29 (br. *d*, *J* = 7, H–N(2.1)); 5.10 (*AB*, *J* = 12, PhCH_2OCON(2.1)); 4.53 (*dd*, *J* = 9, 5, H–C(2.3)); 4.51 (*m*, H–C(2.2)); 4.38 (*m*, *J* = 7, H–C(2.1)); 4.33 (*dd*, *J* = 11, 7, H–C(3.2)); 3.73 (*s*, *Me*O_2C(1.3)); 3.35 (*dd*, *J* = 7, 4, H–C(3.2)); 2.40 (*AB*, *J* = 11, CH_2N(2.2)); 2.20 (*m*, H–C(3.3)); 1.62 (*s*, H–O(3.2)); 1.43 (*d*, *J* = 7, 3 H–C(3.1)); 0.96 (*s*, *t*-BuCH_2N(2.2)); 0.93 (*d*, *J* = 7, 3 H–C(4.3)); 0.90 (*d*, *J* = 7, 3 H–C(4′.3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.1 (*s*); 172.0 (*s*); 170.9 (*s*); 155.6 (*s*); 136.2 (*s*); 128.5 (*d*); 128.2 (*d*); 128.1 (*d*); 67.0 (*t*); 65.5 (*t*); 62.8 (*d*); 61.0 (*t*); 56.8 (*d*); 52.0 (*q*); 49.7 (*d*); 31.5 (*q*); 31.0 (*d*); 27.5 (*q*); 19.1 (*q*); 18.5 (*q*); 17.7 (*q*). FAB-MS: 987 (7, [2*M* + 1]$^+$), 494 (100, [*M* + 1]$^+$), 436 (6), 335 (35), 271 (9), 154 (13), 91 (46). Anal. calc. for $C_{25}H_{37}N_3O_7$: C 61.08, H 7.59, N 8.55, O 22.78; found: C 61.08, H 7.64, N 8.57.

*(2*R*,4*S*)- and (2*S*,4*S*)-2-(*tert*-Butyl)-4-{*N*-[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]carbamoyl}oxazolidine* (**30**; 1:1 diasteroisomeric mixture). Under H_2, 50 mg of Pd on charcoal were added to a soln. of 100 mg (0.24 mmol) of **23** in 30 ml of AcOEt at 0°. The course of the reaction was thoroughly followed by TLC. After no starting material could be detected any more (after *ca.* 1 h), the hydrogenolysis was quenched by the addition of 5 ml of CH_2Cl_2. The mixture was filtered through *Celite*, and the solvents were removed at reduced pressure: 58 mg (84%) of a 1:1 epimeric mixture was obtained.

Data of **30**: ^{1}H-NMR (200 MHz, $CDCl_3$): 7.94 (br. *d*, *J* = 7, NH, 1 diast.); 7.80 (br. *d*, *J* = 8, NH, 1 diast.); 4.46 (*dd*, *J* = 9, 5, C*H*CO_2Me); 4.29 (*s*, H–C(2), 1 diast.); 4.02 (*s*, H–C(2), 1 diast.); 4.13–3.65 (*m*, C*H*CHCO_2Me, H–C(4)); 3.72 (*s*, MeO$_2$C); 2.43 (br. *s*, 1 HN(3)); 1.70 (*m*, H–C(5)); 0.97, 0.94 (2*s*, *t*-Bu); 0.93–0.84 (*m*, *Me*$_2$CHCH). FAB-MS: 573 (7, [2*M* + 1]$^+$), 287 (100, [*M* + 1]$^+$), 229 (17), 130 (27), 71 (15).

$N^{2,2}$,$O^{3,2}$-*Di{[(*tert*-butoxy)carbonyl]phenylalanyl}serylvaline Methyl Ester* (**31**; protons of the two Boc-Phe residues at N(2.2) and O(3.2) are marked by a small N and O, resp., as indeces). To a soln. of 103 mg (0.36 mmol) of **30**, 287 mg (1.08 mmol) of Boc-Phe-OH, and 562 mg (1.08 mmol) of **33** in 5 ml of CH_2Cl_2 were added 0.12 ml (1.08 mmol) of *N*-methylmorpholine. The soln. was allowed to warm up to r.t. After 48 h, acidic workup yielded 120 mg (32%) of **31**.

Data of **31**: $[\alpha]_D^{r.t.} = -7.8$ (*c* = 1.0, MeOH). R_f (Et_2O/pentane 2:1) 0.39. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35–7.12 (*m*, 10 arom. H); 7.04 (br. *d*, *J* = 8, H–N(2.2) or H–N(2.3)); 6.85 (br. *d*, *J* = 7, H–N(2.2) or H–N(2.3)); 4.70–4.35 (*m*, H–C(2.1^O), H–C(2.1^N), H–C(2.2), H–C(3.2), H–C(2.3)); 4.14 (*dd*, *J* = 11, 6, H–C(3.2)); 3.71 (*s*, *Me*O_2C(1.3)); 3.25–3.08 (*m*, 2 H–C(3.1^O)); 3.07 (*m*, 2 H–C(3.1^N)); 2.17 (*m*, H–C(3.3)); 1.41 (*s*, *Me*$_3$COCON(2.1^O)); 1.36 (*s*, *Me*$_3$COCON(2.1^N)); 0.92 (*d*, *J* = 7, 3 H–C(4.3)); 0.91 (*d*, *J* = 7, 3 H–C(4′.3)).

^{13}C-NMR (75 MHz, $CDCl_3$): 171.9 (*s*); 171.8 (*s*); 171.7 (*s*); 168.4 (*s*); 155.5 (*s*); 136.6 (*s*); 136.0 (*s*); 129.2 (*d*); 129.0 (*d*); 128.7 (*d*); 127.2 (*d*); 127.2 (*d*); 127.0 (*d*); 80.4 (*d*); 80.3 (*s*); 63.5 (*t*); 57.7 (*d*); 56.0 (*d*); 54.6 (*d*); 52.2 (*d*); 38.0 (*t*); 37.5 (*t*); 30.9 (*d*); 28.3 (*q*); 28.2 (*q*); 19.0 (*q*); 18.0 (*q*). FAB-MS: 1425 (1, $[2M + 1]^+$), 735 (14, $[M + 23]^+$), 713 (13, $[M + 1]^+$), 613 (33), 557 (9), 513 (14), 348 (15), 219 (10), 164 (16), 120 (100). Anal. calc. for $C_{37}H_{52}N_4O_{10}$: C 62.34, H 7.35, N 7.86, O 22.44; found: C 62.59, H 7.45, N 7.80.

*(2R,4S)-3{(S)-2-[(*tert*-Butoxy)carbonylamino]-3-phenylpropanoyl}-2-(*tert*-butyl)-4-{N-[(S)-1-(methoxycarbonyl)-2-methylpropyl]carbamoyl}oxazolidine* (**32**). To an ice-cooled soln. of 490 mg (2.20 mmol) of **30**, 699 mg (2.64 mmol) of Boc-Phe-OH, and 1.00 g (2.60 mmol) of **34** in 25 ml of DMF, 0.53 ml (4.83 mmol) of *N*-methylmorpholine were added, and the reaction was allowed to warm to r.t. overnight. CH_2Cl_2 was added and the org. phase was washed twice with H_2O and once with each aq. $NaHCO_3$ and aq. NaCl. After drying ($MgSO_4$), the drying agent was removed by filtration. FC gave 346 mg (0.704 mmol) of **32**.

Data of **32**: $[\alpha]_D^{r.t.} = -12.2$ ($c = 1.4$, MeOH). R_f (Et_2O/pentane) 0.35. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.89 (br. *d*, $J = 9$, BocN*H*); 7.35–7.05 (*m*, 5 arom. H); 5.30 (*s*, H–C(2)); 4.96 (br. *d*, 1 BocN*H*); 4.60–4.20 (*m*, BocNHC*H*, H–C(4), H–C(5), C*H*COOMe); 3.72 (*s*, MeO_2C); 3.26 (*dd*, $J = 7$, 4, H–C(5)); 1.40 (*s*, ^{t}BuOCONH); 0.94 (*s*, *t*-Bu-C(2)); 0.94 (*d*, $J = 7$, *Me*CH); 0.89 (*d*, $J = 7$, *Me*CH). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.5 (*s*), 172.4 (*s*); 171.2 (*s*); 155.3 (*s*); 136.2 (*s*); 129.5 (*d*); 129.0 (*d*); 127.5 (*d*); 101.3 (*s*); 80.4 (*s*); 65.9 (*t*); 63.0 (*d*); 61.1 (*t*); 57.0 (*d*); 54.8 (*d*); 52.3 (*s*); 38.7 (*d*); 31.7 (*d*); 31.7 (*s*); 31.2 (*d*); 28.5 (*q*); 27.7 (*q*); 19.3 (*q*); 17.8 (*q*). Anal. calc. for $C_{28}H_{43}N_3O_7$: C 63.02, H 8.12, N 7.87, O 20.99; found: C 62.97, H 8.31, N 7.77.

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