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Stereochemical control in the preparation of α-amino *N*-methylthiazolidine masked aldehydes used for peptide aldehydes synthesis

Christel Gros, Cyril Boulègue, Nathalie Galeotti, Gilles Niel* and Patrick Jouin

UPR9023, CNRS, CCIPE, 141, rue de la Cardonille, 34094 Montpellier Cedex 5, France

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Abstract—Chiral *N*-methyl thiazolidines masked α-amino aldehydes are used for solid phase peptide aldehyde elongation. Contrary to *N*-Boc-protected α-amino aldehydes, *N*-trityl protection secures the chiral integrity of the incoming aldehyde chiral C1′ carbon atom during condensation of the amino aldehydes with L-cysteinyl residues. The Ac-Tyr-Val-Ala-Asp-H caspase inhibitor was prepared on a solid support starting from the *N*-trityl-amino thiazolidine masked aspartinal as a validation of this process.

1. Introduction

Owing to the biological importance of peptide aldehydes as mechanism-based enzyme inhibitors,[1,2] and to their chemical utility for fragments ligation,[3] several C-terminal linkers have been introduced as masked aldehyde templates to perform peptide aldehyde elongation on a solid support.[4,5] As part of our investigations into the preparation of peptide aldehydes,[6] we previously showed that the *N*-methyl thiazolidine ring was a very efficient masked aldehyde precursor.[7] The *N*-methyl thiazolidine ring can be efficiently hydrolyzed under neutral conditions, a known deprotection method used for *N*-methyl thiazoles,[8] and subsequently the target peptide can be recovered from the resin while maintaining both chemical and stereochemical integrity. We reinvestigate herein the preparation of the requisite α-amino acid derived *N*-methyl thiazolidines.[6]

2. Results and discussion

The previously developed synthesis of the head amino thiazolidine residue **A** involved a rather tedious synthetic pathway (route 2, Scheme 1), including the reduction of an intermediate iminium **B** which was constructed via the Mitsunobu cyclization of a thioamide precursor **D**.[6] Though epimerization free, this process is not suitable for large-scale preparations. Therefore we chose the straightforward condensation of an *N*-protected α-amino aldehyde **E** with a cysteinyl derivative **F** (route 1) to construct this intermediate target. Previous related studies involving Boc- or *Z*-*N*-protected α-amino aldehydes favor this pathway since no or little racemization at the C1′ carbon atom has ever been observed or reported.[9–11]

In a first set of experiments we reinvestigated the condensation of *N*-Boc-(*S*)-phenylalaninal[12] with (*R*)-Cys,HCl free acid (Table 1). We observed that this condensation was incomplete under Wyslouch's reaction conditions (i.e. 2 equiv. of pyridine in MeOH, 24 h).[10] Under different reaction conditions ($KHCO_3$ in DMF, 1 h), the starting aldehyde was completely consumed, but ^{1}H NMR analysis of the formed thiazolidine **1** revealed the presence of two C1′ epimeric thiazolidines in a 90:10 ratio. The configuration of both the major (1′*S*,2*R*,4*R*)-**1a** isomer and the minor (1′*R*,2*S*,4*R*)-**1c** isomers was assigned from the ^{1}H NMR literature data.[10] We also confirmed that the (1′*R*,2*S*,4*R*) isomer **1c** was obtained predominantly when starting from *N*-Boc-(*R*)-phenylalaninal. Otherwise, as mentioned by Wyslouch et al.,[11] additional epimerization of C2 occurred when the mixture **1a** and **1c**, obtained from *N*-Boc-(*S*)- or *N*-Boc-(*R*)-phenylalaninal, was allowed to stand several hours or was heated a few minutes in [D_6]DMSO solution. Besides the signals at 4.53 and 4.65 ppm (Table 1), which were attributed to (1′*S*,2*R*,4*R*)-**1a** and (1′*R*,2*S*,4*R*)-**1c**, respectively, by 2D COSY and TOCSY NMR experiments, two significant new signals appeared at 4.57 and 4.50 ppm and might be attributed to **1b** and **1c**, respectively. However a complete interpretation of the spectrum was complicated by the presence of BocNH rotamers.

In order to verify these preliminary results we performed the condensation reaction between *N*-Boc-(*S*)- or *N*-Boc-(*R*)-phenylalaninal and (*R*)-Cys-OMe,HCl (Table 2, entries 1

Keywords: *N*-trityl; thiazolidine; peptide aldehyde; solid phase; ligation.
* Corresponding author. Tel.: +33-467-14-29-70; fax: +33-467-14-29-24; e-mail: niel@ccipe.montp.inserm.fr

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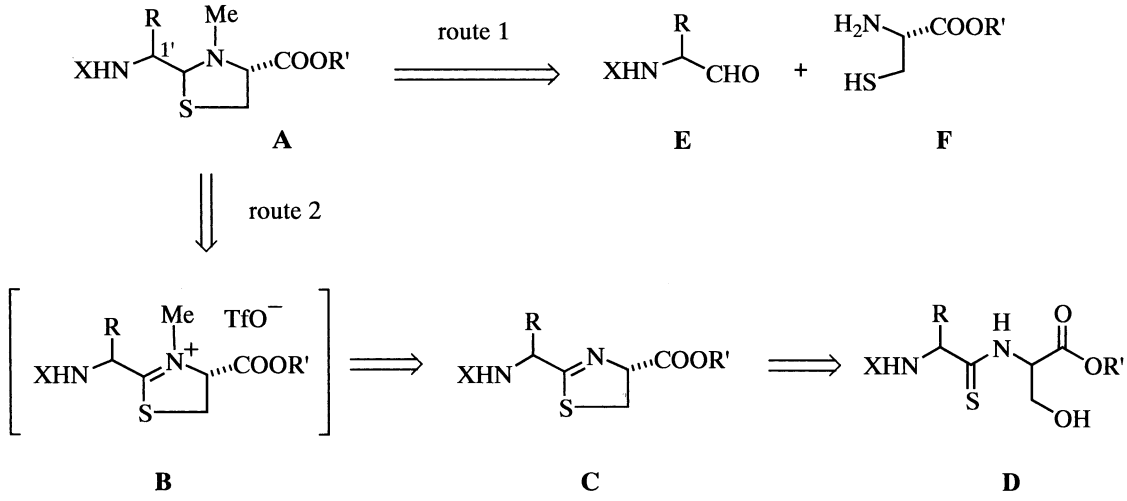
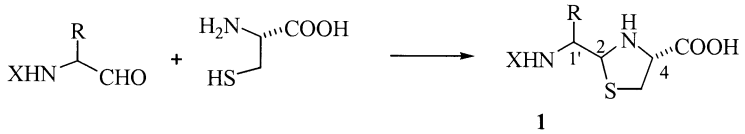


Scheme 1.

Table 1. Selected ^{1}H NMR (δ, ppm) of compounds **1a**, **1d** in [D_6]DMSO solution



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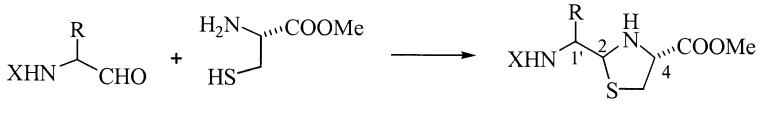
	1a 1′(*S*), 2(*R*), 4(*R*)	**1b**[a] 1′(*S*), 2(*S*), 4(*R*)	**1c** 1′(*R*), 2(*S*), 4(*R*)	**1d**[a] 1′(*R*), 2(*R*), 4(*R*)
BocNH ($J_{NH,1'}$)	6.79 (9.0)	7.00 (7.5)	6.70 (9.4)	6.70 (9.2)
H_2 ($J_{1',2}$)	4.53 (6.0)	4.57 (7.8)	4.65 (7.8)	4.50 (5.8)

[a] After gentle heating for 5 min in the NMR tube.

Table 2. Thiazolidines obtained by condensation of various aldehydes with (*R*)-Cys-OMe,HCl



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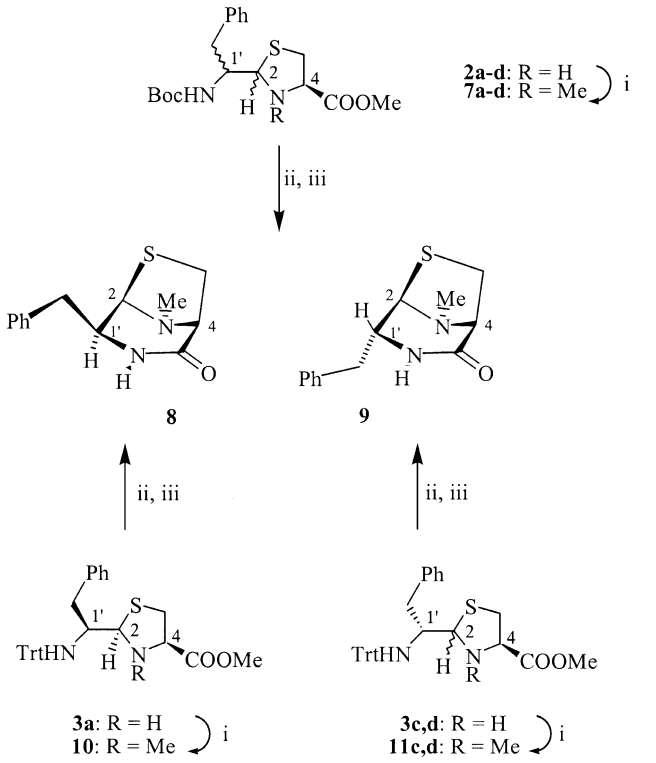
a: 1′(*S*), 2(*R*), 4(*R*); **b**: 1′(*S*), 2(*S*), 4(*R*); **c**: 1′(*R*), 2(*S*), 4(*R*); **d**: 1′(*R*), 2(*R*), 4(*R*)

Entry	Aldehyde	Yield (%)[a]	Diastereoisomers (relative percentages)[b,c]			
1	Boc-(*S*)-Phe-H	86	**2a** (53)	**2b** (11)	**2c** (23)	**2d** (13)
2	Boc-(*R*)-Phe-H	84	**2a** (27)	**2b** (8)	**2c** (38)	**2d** (27)
3	Trt-(*S*)-Phe-H	88	**3a** (100)	**3b** (0)	–[d]	–[d]
4	Trt-(*R*)-Phe-H	92	–[d]	–[d]	**3c** (29)	**3d** (71)
5	Trt-(*S*)-Leu-H	89	**4a** (80)	**4b** (20)	–[d]	–[d]
6	Trt-(*S*)-Asp(O*t*Bu)-H	91	**5a** (55)	**5b** (45)	–[d]	–[d]
7	Trt-(*S*)-Ser(OSEM)-H	85	**6a** (71)	**6b** (29)	–[d]	–[d]

[a] Reaction conditions: 1.5 equiv. (*R*)-Cys-OMe,HCl, 1.5 equiv. $KHCO_3$ (DMF), 1 h, rt.
[b] Ratios were estimated by HPLC (entries 1, 2).
[c] Ratios were estimated by ^{1}H NMR (entries 3–7).
[d] Not observed.

and 2). Here the obtained thiazolidines **2a**–**d** were a mixture of four diastereoisomers including both C2-epimers, from an equilibrium already observed for such thiazolidines,[13] and undesirable C1′-epimers. This latter epimerization could have occurred prior to or during the condensation step, at both the aldehyde and the imine level and was accurately assessed by HPLC analysis. The *cis*-relation between C2 and C4 in thiazolidines **2a** and **2d** was proven by their conversion to the corresponding bicyclic lactams **8** and **9** (Scheme 2).[14] Consequently, we assigned the respective (1′*S*,2*S*,4*R*) and (1′*R*,2*S*,4*R*) configurations to thiazolidines **2a** and **2d**. Therefore, we attempted the synthesis of these target thiazolidines starting from less epimerizable amino aldehydes.

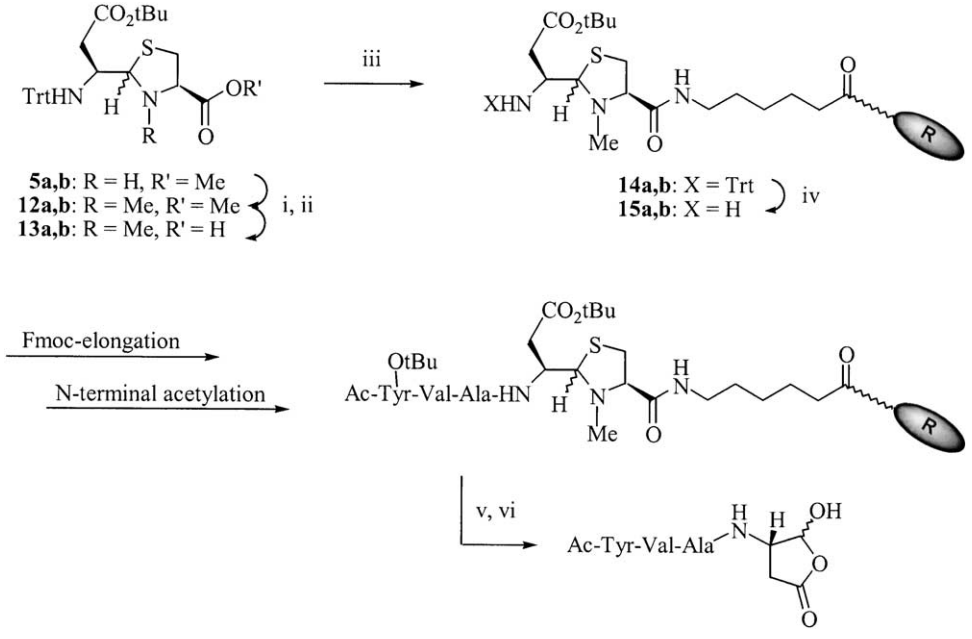
To this end we chose the trityl-protecting amino group since this protecting group prevents partial racemization of *N*-protected α-amino aldehydes,[15,16] possibly by



Scheme 2. *Reagents and conditions*: (i) HCHO, $NaBH_3CN$, AcOH cat.; (ii) TFA, MeOH; (iii) $KHCO_3$, MeOH.

suppressing the deprotonation of the α-center, like the phenylfluorenyl protecting group.[17] In addition, the selective cleavage of the trityl protection under mild acidic conditions is of great value for peptide elongation when the head thiazolidine residue is linked to the resin. Amino aldehydes were prepared by oxidation of their corresponding alcohols according to the procedure described by Albeck[16] and condensed with (*R*)-Cys-OMe,HCl under the above conditions. All the *N*-trityl-α-amino aldehydes we tested led cleanly and with good yields to the desired thiazolidines without observable C1′ epimerization. This was demonstrated in the case of *N*-trityl-(*S*)- or (*R*)-phenylalaninal (entries 3, 4) since each individual condensation with (*R*)-Cys-OMe,HCl led to fully distinct diastereoisomers. Condensation of *N*-trityl-(*S*)-phenylalaninal appears to be a marginal case, leading to a single isomer (1′*S*,2*R*,4*R*)-**3a**, (probably due to a favorable matched pair of reactants), whereas the *N*-trityl-(*R*)-phenylalaninal produced a pair of C2 epimers (1′*R*,2*S*,4*R*)-**3c** and (1′*R*,2*R*,4*R*)-**3d** in a 29:71 ratio. Thus, contrary to what Wyslouch et al. observed with the Boc protection,[11] the predominant (*R*) configuration at C2 was introduced independently of the incoming *N*-trityl-protected aldehyde chirality. In addition, on storage in [D_6]DMSO solution or after rapid heating in the NMR tube, we did not observe any evolution of the pure compound **3a** or of the mixture of compounds **3c** and **3d**. Condensation of Trt-(*S*)-Leu-H, Trt-(*S*)-Asp(O*t*Bu)-H and Trt-(*S*)-Ser(OSEM)-H under the same conditions as for *N*-Trt-(*S*)-Phe-H also favored the formation of the major (2*R*)-epimer, though in variable proportions (entries 5–7). We verified that compounds **4a**, **5a** and **6a** possessed a *cis*-configurated thiazolidine ring since strong H2–H4 correlations were observed by NOESY experiments.

As for thiazolidines **2a** and **2d**, we ascertained the absolute configuration at the C2 position by performing the internal cyclization of the *N*-methyl compounds **10** and **11c**, **d** resulting from **3a** and **3d**, respectively.[18] After TFA-assisted removal of the C1′ trityl protecting group of **3a** and cyclization of the resulting primary amine, the bicyclic thiazolidinyl lactam **8** was obtained in 95% yield as the sole product. A similar reaction sequence starting from the mixture of compounds **3c**, **d** led exclusively to the transformation of **3d** into the bicyclic lactam **9** since only the C2 and C4 substituents, possessing a *cis* relationship,



Scheme 3. *Reagents and conditions*: (i) HCHO, $NaBH_3CN$, AcOH cat.; (ii) NaOH 1N, dioxane/water (73% over two steps); (iii) ε-Ahx-Met-Expansin® resin, BOP, HOBt, DIEA, DCM; (iv) 1% TFA in MeOH; (v) TFA/water (95:5); (vi) CuO (14 equiv.), $CuCl_2$ (9 equiv.), CH_3CN/water/DMF (1:1:2) (54% from **13**).

allowed a bicyclic topology. We also observed by NMR analysis that the free amine intermediate derived from the detritylation of **3c** did not evolve even after standing 48 h at room temperature in [D_5]pyridine. This further demonstrated that there was no observable C2 equilibration of the unprotected amino thiazolidine under these conditions.

To evaluate the ability of these *N*-trityl-amino thiazolidines to serve as precursors for the synthesis of peptide aldehydes on solid support, we prepared the Ac-Tyr-Val-Ala-Asp-H caspase inhibitor.[2,19,20] Prepared from BocAsp(O*t*Bu)H, the mixture of thiazolidines **5a**, **b** was *N*-methylated[18] to **12a**, **b** (Scheme 3) which was then saponified to give the *N*-methyl thiazolidine **13a**, **b** (overall yield: 72%). Coupling of compound **13a**, **b** to the Met-Expansin® resin was performed through 6-amino-hexanoic acid as a spacer.[7] Deprotection of the tritylamino group was performed under mild acid conditions. Fmoc-strategy was chosen for elongation to the masked tetrapeptide aldehyde. The final cleavage step was successfully performed as previously described[6,8] using a mixture of copper salts which enabled the isolation of Ac-Tyr-Val-Ala-Asp-H in a 54% overall yield from **13a**, **b**. The crude product was estimated to be 90% pure by analytical HPLC and its ^{1}H NMR data were favorably compared to literature data.[19] Slow epimerization of the final product in [D_4]MeOH was only observed after standing at room temperature for one day. MALDI-TOF mass spectrometry, in the positive mode, revealed two major signals corresponding to $[M+Na]^+$ and $[M-H+2\times Na]^+$, the latter of which was presumably related to the presence of a carboxylate sodium salt.

In conclusion, the preparation of *N*-methyl-thiazolidinyl-derived amino aldehydes was improved by direct condensation of *N*-protected amino aldehydes with L-cysteinyl residues.[6] We have shown that whereas the straightforward condensation of Boc-protected amino aldehydes with (*R*)-cysteinyl residues gives an uncontrollable level of epimerization of the incoming aldehyde chiral center, the use of *N*-tritylamino aldehydes dramatically secures the stereochemical integrity of the final thiazolidine derivatives. This methodology was successfully applied to the solid phase synthesis of a model peptide and offers a viable alternative to the preparation of peptide aldehydes.

3. Experimental

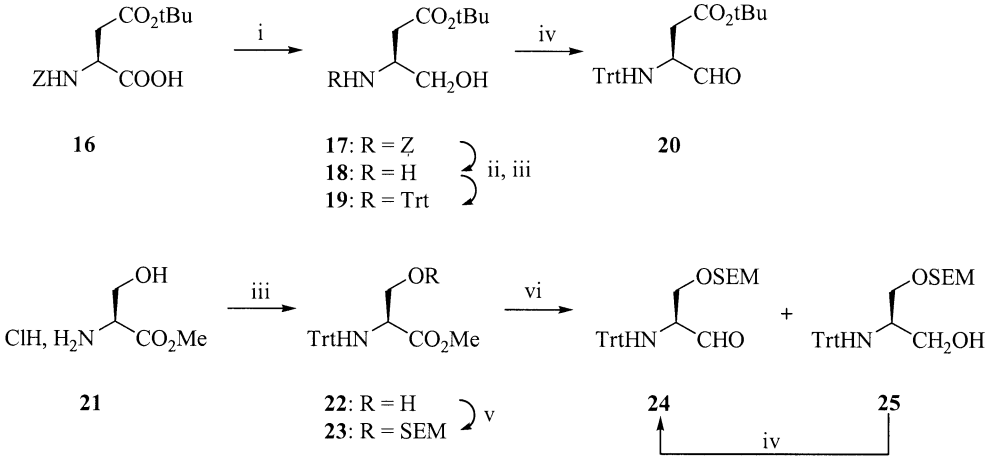
3.1. General

^{1}H NMR spectra were recorded at 200 MHz on a Bruker Avance-DPX and chemical shifts are reported in ppm. Mass spectra were performed either in the FAB^+ mode, unless otherwise noted, by the Department of Physical Measurements of the University of Montpellier II or using MALDI-TOF mass spectrometry, in the positive mode, on a Bruker Biflex III and DHB as a matrix. Optical rotations were run at 20°C. Column chromatography was conducted by using silica gel (70–230 or 240–400 mesh) as the stationary layer. Analytical TLC was performed on silica gel 60F254 aluminum sheets. Analytical HPLC was carried out with a Kromasil C8 column (5 μm; 4.6×150 mm) using a linear gradient of acetonitrile+0.1% TFA (solvent B) in water+0.1% TFA (solvent A) at a flow rate of 1.5 mL/min (conditions A). Usual work-up A consisted in (i) dissolving the residue in AcOEt, (ii) several successive washings of the organic phase with $NaHCO_3$ (5% aqueous solution), $KHSO_4$ (5% aqueous solution) and brine, (iii) drying the organic phase over sodium sulfate, (iv) evaporation of the solvent under reduced pressure. Usual work-up B is similar to work-up A except that the order of treatment with $NaHCO_3$ and $KHSO_4$ was reversed.

3.2. Preparation of the *N*-protected amino aldehydes

N-Boc-(*S*)-, *N*-Boc-(*R*)-phenylalaninal were prepared by reduction of their respective esters according to Fehrentz's procedure.[12] All *N*-Boc protected α-amino aldehydes were used without purification and condensed immediately with the appropriate cysteinyl residue.

N-Trityl-(S)-phenylalaninal, N-trityl-(R)-phenylalaninal, N-trityl-(S)-leucinal. These compounds were prepared according to Albeck[16] and could be stored at 0°C for three months without loss of optical purity.



Scheme 4. *Reagents and conditions*: (i) $ClCO_2iBu$, NMM, DME then $NaBH_4$, water; (ii) H_2, Pd/C, abs. EtOH (73% over two steps); (iii) TrtCl, NEt_3, DCM; (iv) Swern's oxidation; (v) SEMCl, DIEA, DCM; (vi) Dibal, toluene.

*N-Trityl-(S)-aspartinal 4-tert-butyl ester (**20**)*. This aldehyde was prepared in four steps starting from *N-Z*-aspartinol 4-*tert*-butyl ester **17** (Scheme 4), itself obtained by reduction of **16** according to the procedure of Rodriguez et al.[21]

3.2.1. (*S*)-Aspartinol 4-*tert*-butyl ester (18). Hydrogenation of compound **17** (4.2 g, 13.6 mmol) was performed using palladium on charcoal (0.42 g) under a hydrogen atmosphere in abs EtOH (110 mL) for 4 h. Evaporation of the solvent furnished the amino alcohol **18** as an oil. This product was used in the next step without further purification. Yield: 99%; ^{1}H NMR ([D_6]DMSO) δ=3.27–3.12 (m, 2H), 2.97 (m, 1H), 2.31 (dd, J=15.0, 4.8 Hz), 2.01 (dd, J=15.0, 8.4 Hz), 1.41 (s, 9H).

3.2.2. *N*-Trityl-(*S*)-aspartinol 4-*tert*-butyl ester (19). Amino alcohol **18** (2.15 g, 12.3 mmol) and NEt_3 were dissolved in dry CH_2Cl_2 (60 mL). To the ice-bath cooled preceding solution, trityl chloride (3.43 g, 12.3 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise over 15 min. After stirring 1 h at rt the solvent was evaporated and the residue dissolved in AcOEt (100 mL). Work-up B followed by a flash column chromatography purification (AcOEt/cyclohexane 80:20) furnished alcohol **19** as an oil. Yield: 83%; ^{1}H NMR ($CDCl_3$) δ=7.59–7.54 (m, 6H), 7.30–7.17 (m, 9H), 3.42 (dd, J=11.0, 4.0 Hz, 1H), 3.14 (dd, J=11.0, 6.0 Hz, 1H), 2.99 (m, 1H), 2.58 (bs, 1H), 1.88 (dd, J=15.7, 3.5 Hz, 1H), 1.78 (dd, J=15.7, 6.3 Hz, 1H), 1.39 (s, 9H); MS (FAB$^+$); *m/z* (%): 418 (6), 360 (4), 340 (4), 307 (5), 277 (13), 243 (36), 185 (100); $[\alpha]_D^{20}$=+7.6 (c=1, MeOH); Anal. calcd for $C_{27}H_{29}NO_3$: C, 78.03; H, 7.04; N, 3.37. Found: C, 78.25; H, 7.20; N, 3.43.

3.2.3. *N*-Trityl-(*S*)-aspartinal 4-*tert*-butyl ester (20). Swern's procedure[22] was used to perform the oxidation of compound **19**. Yield: 98%; ^{1}H NMR ($CDCl_3$) δ=9.19 (s, 1H), 7.60–7.55 (m, 6H), 7.37–7.21 (m, 9H), 3.41 (dd, J=6.0, 3.2 Hz, 1H), 2.63 (dd, J=16.4, 3.2 Hz, 1H), 2.16 (dd, J=16.4, 6.0 Hz, 1H), 1.77 (bs, 1H), 1.46 (s, 9H); MS (FAB$^+$); *m/z* (%): 416 (8), 358 (6), 338 (5), 243 (100), 57 (42).*N-Trityl-(S)-serinal 3-[2-(trimethylsilyl)-ethoxymethyl ether] (**24**)*. This aldehyde was prepared from serine methyl ester hydrochloride **21** in three steps (Scheme 4).

3.2.4. *N*-Trityl-(*S*)-serine methyl ester (22). The trityl group was introduced similarly as for compound **18**. The resulting trityl amino derivative **22** was obtained as a solid after work-up B and purification by flash column chromatography (AcOEt/cyclohexane 80:20). Yield: 92%; ^{1}H NMR ([D_6]DMSO) δ=7.44–7.35 (m, 6H), 7.32–7.15 (m, 9H), 4.94 (t, J=6.0 Hz, 1H), 3.50 (dd, J=10.6, 3.0 Hz, 1H), 3.42 (dd, J=10.6, 6.6 Hz, 1H), 3.21 (m, 1H), 3.12 (s, 3H), 2.80 (d, J=10.0 Hz, 1H); MS (FAB$^+$); *m/z* (%): 362 (15), 344 (6), 330 (5), 243 (100); mp 147°C (lit. mp 146°C);[23] $[\alpha]_D^{20}$=+12.3 (c=1.2, MeOH); Anal. calcd for $C_{23}H_{23}NO_3$: C, 76.42; H, 6.42; N, 3.88. Found: C, 76.22; H, 6.28; N, 3.75.

3.2.5. *N*-Trityl-(*S*)-serine 3-[2-(trimethylsilyl)-ethoxymethyl ether] methyl ester (23). A mixture of compound **22** (3.61 g, 10 mmol), DIEA (5.2 mL, 30 mmol) and 2-(trimethylsilyl)-ethoxy)-methyl chloride (2.66 mL, 15 mmol) was stirred overnight at rt in CH_2Cl_2. The solvent was evaporated under reduced pressure. Work-up B furnished compound **23** as an oil which was sufficiently pure for the next step. Yield: 97%; ^{1}H NMR ([D_6]DMSO) δ=7.44–7.40 (m, 6H), 7.32–7.16 (m, 9H), 4.52 (s, 2H), 3.60–3.43 (m, 3H), 3.35 (m, 2H), 3.17 (s, 3H), 2.91 (d, J=9.8 Hz, 3H), 2.80 (d, 1H), 0.83 (t, J=7.4 Hz, 2H), −0.01 (s, 9H); MS (FAB$^+$); *m/z* (%): 491 (13), 459 (6), 398 (9), 369 (5), 243 (100); $[\alpha]_D^{20}$=−9.6 (c=1.05, MeOH).

3.2.6. *N*-Trityl-(*S*)-serinal 3-[2-(trimethylsilyl)-ethoxymethyl ether] (24). To a solution of ester **23** (4.61 g, 9.4 mmol) in dry toluene (100 mL) cooled at −75°C was added Dibal (20.6 mL; 1 M/toluene) over a 30-minute period. The temperature was allowed to reach −45°C, then MeOH (5 mL) was added dropwise. After room temperature had been reached, the solvent was evaporated under reduced pressure. Diethyl ether (80 mL) was added to the residue, and the organic phase was washed twice successively with cold 1N HCl (40 mL), a 5% aqueous solution of $NaHCO_3$ (40 mL) and brine (40 mL) and was dried over sodium sulfate. The oily residue was purified by flash column chromatography (AcOEt/cyclohexane 90:10) to give aldehyde **24** (2.46 g, 5.33 mmol) and alcohol **25** (1.23 g, 2.65 mmol); this latter compound could be oxidized to aldehyde **24** in the same way as were the tritylamino aldehydes. Yield: 57%; ^{1}H NMR ($CDCl_3$) δ=9.31 (d, J=0.8 Hz, 1H), 7.56–7.49 (m, 6H), 7.33–7.16 (m, 9H), 4.52 (q, AB system, J=6.8 Hz, 2H), 3.70 (dd, J=9.6, 3.6 Hz, 1H), 3.52 (dd, J=11.8, 10.0 Hz, 2H), 3.41 (m, 1H), 3.06 (dd, J=9.6, 5.2 Hz, 1H), 0.89 (m, 2H), 0.01 (s, 9H); MS (FAB$^+$); *m/z* (%): 463 (9), 433 (5), 370 (12), 341 (7), 243 (100).

3.3. Preparation of thiazolidines (2–6)

To a stirred solution of protected aldehyde (1 mmol) in DMF, was added a freshly prepared aqueous solution of H-Cys-OMe,HCl (1.5 mmol) and $KHCO_3$ (1.5 mmol) at 5°C. The reaction mixture was further stirred for 1 h at rt and diluted with brine. The aqueous phase was extracted three times with diethyl ether or AcOEt. The combined organic extracts were dried over sodium sulfate and the solvent was evaporated. The residue was purified by flash column chromatography (AcOEt/cyclohexane).

3.3.1. Thiazolidines (2a–d). These compounds were not separable by flash column chromatography. The crude condensation mixtures obtained from *N*-Boc-(*S*)-, respectively, *N*-Boc-(*R*)-phenylalaninal were studied by HPLC and ^{1}H NMR spectrometry (Table 3).

Table 3. Selected ^{1}H NMR and HPLC data of compounds **2a–d**

	2a	**2b**	**2c**	**2d**
^{1}H NMR, δ OCH_3 (ppm)[a]	3.69	3.70	3.66	3.64
HPLC, t_R (min)[b]	5.91	5.61	5.41	5.10

[a] Recorded in [D_6]DMSO.
[b] Gradient: 50–70% solvent B in 10 min.

3.3.2. Thiazolidine (3a). Yield: 88%; ^{1}H NMR ($CDCl_3$) δ=7.60–7.55 (m, 6H, Ar), 7.38–7.14 (m, 12H, Ar), 6.91

(m, 2H, Ar), 4.32 (d, J=9.8 Hz, 1H, H_2), 3.80 (s, 3H, OCH_3), 3.72–3.53 (m, 2H, H_4, NHcycle), 3.36 (m, 1H, $H_{1'}$), 3.27 (dd, J=10.6, 5.8 Hz, 1H, H_5), 2.91 (d, J=9.2 Hz, 1H, N*H*Trt), 2.82 (dd, J=10.6, 6.2 Hz, H_5), 2.45 (dd, J=13.2, 4.0 Hz, 1H, $H_{2'}$), 2.15 (dd, J=13.2, 10.8 Hz, 1H, $H_{2'}$); MS (FAB^+); *m/z* (%): 509 (16), 461 (4), 431 (4), 307 (10), 277 (42), 243 (100); mp 149°C; $[\alpha]_D^{20}=-12.1$ (c=1.9, $CHCl_3$); Anal. calcd for $C_{32}H_{32}N_2O_2S$: C, 75.56; H, 6.34; N, 5.51. Found: C, 75.45; H, 6.20; N, 5.42.

3.3.3. Thiazolidines (3c, d). The mixture of these unseparated oily compounds was obtained in a combined yield of 92%; ^1H NMR ($CDCl_3$) for **3d**, δ=7.62 (m, 6H, Ar), 7.35–7.17 (m, 12H, Ar), 6.72 (m, 2H, Ar), 4.49 (m, 1H, H_2), 3.86 (s, 3H, OCH_3), 3.69 (dd, J=9.8, 6.4 Hz, 1H, H_4), 3.23 (m, 1H, $H_{1'}$), 3.21 (dd, J=10.0, 6.4 Hz, 1H, H_5), 2.75 (dd, J=10.0, 9.8 Hz, 1H, H_5), 2.67 (m, 2H, $H_{2'}$); MS (FAB^+); *m/z* (%): 509 (8), 491 (2), 461 (7), 431 (6), 369 (14), 277 (33), 243 (100).

3.3.4. Thiazolidines (4a, b). The mixture of these unseparated compounds was obtained in a combined yield of 89%. Some of the ^1H NMR signals were common to both epimers **6a** and **6b** except those assigned to H_2, H_4, $H_{4'}$ and OCH_3, ^1H NMR ([D_6]DMSO) for **4a**, δ=7.48–7.41 (m, 6H, Ar), 7.30–7.10 (m, 12H, Ar), 4.59 (dd, J=12.1, 2.6 Hz, 1H, H_2), 3.81 (m, 1H, H_4), 3.71 (s, 3H, OCH_3), 3.57 (m, 1H, NH_{cycle}), 3.17 (dd, J=10.2, 7.3 Hz, 1H, H_5), 2.99 (m, 1H, $H_{1'}$), 2.72 (dd, J=10.2, 9.4 Hz, 1H, H_5), 2.55 (d, J=10.1 Hz, 1H, NH_{CPh3}), 1.42–1.20 (m, 1H, $H_{3'}$), 1.11–0.79 (m, 1H, $H_{2'}$), 0.46 (d, J=6.3 Hz, 3H, $H_{4'}$), 0.45 (m, 1H, $H_{2'}$), 0.44 (d, J=6.5 Hz, 3H, $H_{4'}$); MS (FAB^+); *m/z* (%): 475 (3), 429 (7), 381 (6), 349 (9), 307 (19), 243 (100). ^1H NMR ([D_6]DMSO) for **4b**, δ=7.48–7.41 (m, 6H, Ar), 7.30–7.10 (m, 12H, Ar), 4.75 (dd, J=10.9, 3.6 Hz, 1H, H_2), 4.30 (m, 1H, H_4), 3.57 (s, 3H, OCH_3), 3.57 (m, 1H, NH_{cycle}), 3.49 (m, 1H, H_5), 2.99 (d, J=5.1 Hz, 1H, H_5), 2.83 (s, 1H, NH_{CPh3}), 2.21 (m, 1H, $H_{1'}$), 1.42–1.20 (m, 2H, $H_{2'}/H_{3'}$), 1.11–0.79 (m, 1H, $H_{2'}$), 0.51 (d, J=6.0 Hz, 3H, $H_{4'}$), 0.31 (d, J=6.3 Hz, 3H, $H_{4'}$).

3.3.5. Thiazolidines (5a, b). The mixture of these unseparated compounds was obtained in a combined yield of 91% Some of the ^1H NMR signals were common to both epimers **6a** and **6b** except those assigned to H_2, H_4 and OCH_3; ^1H NMR ([D_5]Pyridine) for **5a**, δ=7.78 (m, 6H, Ar), 7.34–7.13 (m, 12H, Ar), 5.58 (d, J=5.6 Hz, 1H, H_2), 4.22 (dd, J=6.1, 6.1 Hz, 1H, H_4), 3.64 (s, 3H, OCH_3), 3.34 (m, 1H, $H_{1'}$), 3.21 (dd, J=10.4, 6.1 Hz, 1H, H_5), 3.03 (dd, J=10.4, 6.1 Hz, 1H, H_5), 2.17 (dd, J=15.9, 7.7 Hz, 1H, $H_{2'}$), 2.17 (dd, J=15.9, 2.7 Hz, 1H, $H_{2'}$), 1.38 (s, 9H, *t*Bu); MS (FAB^-); *m/z* (%): 533 (4), 461 (7), 369 (9), 307 (8), 277 (18), 243 (25), 185 (100), 93 (46). ^1H NMR ([D_5]Pyridine) for **5b**, δ=7.78 (m, 6H, Ar), 7.34–7.13 (m, 12H, Ar), 4.88 (d, J=4.8 Hz, 1H, H_2), 3.95 (dd, J=8.5, 6.2 Hz, 1H, H_4), 3.81 (m, 1H, $H_{1'}$), 3.61 (s, 3H, OCH_3), 3.41 (dd, J=9.7, 8.5 Hz, 1H, H_5), 2.96 (dd, J=9.7, 6.1 Hz, 1H, H_5), 2.23 (m, 2H, $H_{2'}$), 1.37 (s, 9H, *t*Bu).

3.3.6. Thiazolidines (6a, b). The mixture of these unseparated compounds was obtained in a combined yield of 91%. Some of the ^1H NMR signals were common to both epimers **6a** and **6b** except those assigned to H_2, $H_{3'}$ and OCH_3; ^1H NMR ([D_6]DMSO) for **6a**, δ=7.50 (m, 6H, Ar), 7.34–7.18 (m, 12H, Ar), 4.63 (dd, J=12.1, 2.4 Hz, 1H, H_2), 4.35 (d, J=6.6 Hz, 1H, $H_{3'}$), 4.11 (d, J=6.6 Hz, 1H, $H_{3'}$), 3.71 (m, 1H, $H_{4'}$), 3.70 (s, 3H, OCH_3), 3.43–3.31 (m, 3H, $NH_{cycle}/H_{4'}$), 3.24–3.15 (m, 2H, $H_{2'}/H_5$), 2.99 (m, 1H, $H_{1'}$), 2.74–2.62 (m, 1H, H_5), 2.34 (dd, J=9.2, 6.2 Hz, 1H, $H_{2'}$), 0.76 (m, 2H, $H_{5'}$), −0.05 (s, 9H, $SiMe_3$); MS (FAB^+); *m/z* (%): 547 (3), 469 (7), 386 (9), 315 (9), 243 (100). ^1H NMR ([D_6]DMSO) for **6b**, δ=7.50 (m, 6H, Ar), 7.34–7.18 (m, 12H, Ar), 4.90 (dd, J=8.0, 8.0 Hz, 1H, H_2), 4.46 (d, J=6.4 Hz, 1H, $H_{3'}$), 4.21 (d, J=6.4 Hz, 1H, $H_{3'}$), 3.67 (s, 3H, OCH_3), 3.55 (m, 1H, NH_{cycle}), 3.43–3.31 (m, 1H, $H_{4'}$), 3.24–3.15 (m, 1H, $H_{2'}$), 2.99–2.91 (m, 1H, H_5), 2.81 (m, 1H, $H_{2'}$), 2.74–2.62 (m, 1H, H_5), 2.09 (m, 1H, $H_{1'}$), 0.76 (m, 2H, $H_{5'}$), −0.03 (s, 9H, $SiMe_3$).

3.4. Preparation of *N*-methyl thiazolidines (7a–d), (10), (11c–d) and (12a, b)

To a stirred solution of the thiazolidine **2a–d**, **3a**, **3c**, **d** or **5a**, **b** (1 mmol) in CH_3CN/CH_2Cl_2 (3:1, 2 mL) was added successively an aqueous solution of formaldehyde (6 mmol) and sodium cyanoborohydride (1.6 mmol) in one portion at rt. Acetic acid (50 μL) was added four times to the mixture until disappearance in about 30 min of the starting material as determined by TLC. The solvent was evaporated and work-up A led to the title compounds after purification by flash column chromatography.

3.4.1. Thiazolidine (7a–d). Obtained from **2a–d** as a mixture of four diastereoisomers which was directly used for the preparation of bicyclic lactams **8** and **9** (see below). Yield: 89%.

3.4.2. Thiazolidine (10). Solid, obtained from **3a** as a single diastereoisomer. Yield: 94%; ^1H NMR ($CDCl_3$) δ=7.73 (m, 6H), 7.36–7.09 (m, 12H), 6.74 (m, 2H), 3.58 (s, 3H), 3.51 (d, J=2.4 Hz, 1H, NH), 3.50–3.37 (m, 2 H, H_4/H_5), 3.29 (d, J=5.2 Hz, 1H, H_2), 3.11 (dd, J=8.2, 3.4 Hz, 1H, H_5), 2.65 (m, 1H, $H_{1'}$), 2.55 (dd, J=13.6, 3.6 Hz, 1H, $H_{2'}$), 2.29 (dd, J=13.6, 11.2 Hz, 1H, $H_{2'}$), 1.91 (s, 3 H); MS (FAB^+); *m/z* (%): 523 (7), 445 (5), 307 (39), 289 (21), 243 (100); mp 169–170°C; $[\alpha]_D^{20}=+95$ (c=2.01, $CHCl_3$); Anal. calcd for $C_{33}H_{34}N_2O_2S$: C, 75.83; H, 6.56; N, 5.36. Found: C, 75.63; H, 6.46; N, 5.28.

3.4.3. Thiazolidines (11c, d). Oil, obtained from **3c**, **d** as a mixture of inseparable diastereoisomers. Yield: 92%; most ^1H NMR signals were common to both epimers **11c** and **11d** except those assigned to H_2, OCH_3 and NCH_3. ^1H NMR for **11c** ($CDCl_3$) δ=7.76–7.64 (m, 6H), 7.39–7.12 (m, 12H), 6.79 (m, 2H), 3.99 (d, J=1.6 Hz, 1H, H_2), 3.71 (s, 3H), 3.46 (dd, J=8.2, 6.4 Hz, 1H, H_4), 3.37 (dd, J=10.5, 6.4 Hz, 1H, H_5), 3.18 (dd, J=10.5, 8.2 Hz, 1H, H_5), 3.07 (m, 1H, $H_{1'}$), 2.68 (d, J=9.2 Hz, 1H, NH), 2.34 (dd, J=12.6, 2.4 Hz, 1H, $H_{2'}$), 2.29 (dd, J=12.6, 7.8 Hz, 1H, $H_{2'}$), 2.08 (s, 3H); MS (FAB^+); *m/z* (%): 523 (5), 445 (6), 307 (35), 289 (15) 243 (100).

3.4.4. Thiazolidines (12a, b). Oil, obtained from **5a**, **b** as a mixture of inseparable diastereoisomers. Yield: 88%; only aromatic and NCH_3 ^1H NMR signals were common to both

epimers **12a** and **12b**; ^{1}H NMR for **12a** ($CDCl_3$) δ=7.83–7.65 (m, 6H), 7.35–6.94 (m, 14H), 4.62 (d, J=3.4 Hz, 1H, H_2), 3.99 (d, J=4.8 Hz, 1H, H_4), 3.82 (s, 3H), 3.60 (m, 1H, $H_{1'}$), 3.22 (dd, J=10.6, 4.8 Hz, 1H, H_5), 2.95 (d, J=10.6 Hz, 1H, H_5), 2.40 (s, 3H, NCH_3), 2.27 (dd, J=15.2, 9.6 Hz, 1H, $H_{2'}$), 1.41 (s, 9H), 1.20 (dd, J=15.2, 1.8 Hz, 1H, $H_{2'}$); MS (FAB^-); m/z (%): 547 (4), 469 (7), 386 (12), 243 (100), 57 (9). ^{1}H NMR for **12b** ($CDCl_3$) δ=7.83–7.65 (m, 6H), 7.35–6.94 (m, 14H), 4.15 (d, J=2.8 Hz, 1H, H_2), 3.75 (m, 1H, H_4), 3.72 (s, 3H), 3.48 (dd, J=10.2, 9.8 Hz, 1H, H_5), 3.02 (m, 2H, $H_{1'}/H_5$), 2.40 (s, 3H, NCH_3), 1.83 (d, J=6.2 Hz, 2H, $H_{2'}$), 1.40 (s, 9H).

3.5. Preparation of bicyclic lactams (8) and (9)

3.5.1. Lactams (8) and (9). Compounds **7a–d** (380 mg, 1 mmol) were stirred in trifluoroacetic acid (0.7 mL, 10 mmol) for 40 min. After evaporation of the acid, MeOH (2 mL) and $KHCO_3$ (10 mg, 1 mmol) were added to the reaction mixture which was stirred for 4 h at rt. The solvent was evaporated and the residue dissolved in AcOEt. The organic phase was washed three times with brine then dried over sodium sulfate. The solvent was evaporated and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH 98:2), affording pure compounds **12** and **13** in a ratio of 9:1. Yield: 54%. Analytical data are given below.

3.5.2. Lactam (8). To compound **10** (330 mg, 0.63 mmol) dissolved in CH_2Cl_2/methanol (1:1, 1.5 mL) was added trifluoroacetic acid (15 μL, 0.22 mmol). After 15 min solid $KHCO_3$ (10 mg, 1 mmol) was added and the mixture was stirred for 2 h at rt. The solvent was evaporated and the residue was dissolved in AcOEt. The organic phase was washed three times with brine then dried over sodium sulfate. The solvent was evaporated leaving the expected product as a solid residue. Yield: 75%; ^{1}H NMR ([D_6]DMSO) δ=7.60 (s, 1H, NH), 7.37–7.13 (m, 5H), 4.17 (dd, J=1.6, 1.6 Hz, 1H, H_5), 3.88 (m, 1H, H_4), 3.83 (d, J=5.0 Hz, 1H, H_1), 3.08 (dd, J=12.5, 5.6 Hz, 1H, H_8), 2.92 (d, J=5.0 Hz, 1H, H_8), 2.83 (dd, J=12.0, 4.8 Hz, 1H, $H_{1'}$), 2.70 (dd, J=12.0, 11.0 Hz, 1H, $H_{1'}$), 2.10 (s, 3 H); MS (FAB^+); m/z (%): 249 (100), 203 (20), 201 (25), 158 (3), 111 (23), 91 (15); mp 150–151°C; $[\alpha]_D^{20}$=−52.4 (c=2.12, $CHCl_3$); Anal. calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.79; H, 6.48; N, 11.35.

3.5.3. Lactam (9). The above procedure was repeated starting from the mixture of thiazolidines **11c**, **d**, furnishing lactam **9** as a white solid after purification by flash column chromatography (CH_2Cl_2/MeOH 98:2). Yield: 63%; ^{1}H NMR ([D_6]DMSO) δ=7.62 (s, 1H, NH), 7.38–7.17 (m, 5H), 4.40 (d, J=1.0 Hz, 1H, H_5), 3.86 (dd, J=5.3, 0.8 Hz, 1H, H_1), 3.29 (m, 1H, H_4), 3.11 (dd, J=10.6, 5.3 Hz, 1H, H_8), 3.01 (dd, J=10.6, 0.7 Hz, 1H, H_8), 2.88 (dd, J=13.1, 5.9 Hz, 1H, $H_{1'}$), 2.81 (dd, J=13.1, 8.3 Hz, 1H, $H_{1'}$), 2.16 (s, 3H); MS (FAB^+); m/z (%): 249 (100), 203 (14), 201 (32), 158 (4), 111 (26), 91 (25); mp 138–139°C; $[\alpha]_D^{20}$=−25.6 (c=1.02, $CHCl_3$); Anal. calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.75; H, 6.36; N, 11.18.

3.6. Preparation of Ac-Tyr-Val-Ala-Asp-H

3.6.1. Thiazolidine (13a, b). Thiazolidine **12a**, **b** (874 mg, 1.6 mmol) in dioxane (10 mL) was saponified for 3 h at +10°C by 1N NaOH (8 mL, 8 mmol). The reaction mixture was acidified with a 5% aqueous solution of $KHSO_4$ and the dioxane was evaporated. The residue was extracted three times with AcOEt and the organic phases were dried over sodium sulfate. Filtration of the dessicant and evaporation of the solvent gave the expected product as oil and a mixture of diastereoisomers in a 1:1 ratio. Yield: 63% Aromatic, NCH_3 and OtBu ^{1}H NMR signals were common to both epimers **13a** and **13b**; ^{1}H NMR ([D_6]DMSO) for **13a** δ=7.54–7.42 (m, 6H), 7.37–7.10 (m, 10H), 3.90 (d, J=3.0 Hz, 1H, H_2), 3.60 (m, 2H, H_4/H_5), 3.22 (d, J=6.8 Hz, 1H, H_5), 2.88 (m, 1H, $H_{1'}$), 2.47 (d, J=8.8 Hz, 1H, NH), 1.35 (dd, J=10.4, 7.6 Hz, 1H, $H_{2'}$), 1.23 (s, 9H), 1.16 (dd, J=10.4, 7.0 Hz, 1H, $H_{2'}$); MS (FAB^+); m/z (%): 533 (10), 489 (8), 477 (15), 433 (25), 271 (33), 243 (100), 57 (45). ^{1}H NMR ([D_6]DMSO) for **13b** δ=7.54–7.42 (m, 6H), 7.37–7.10 (m, 10H), 4.37 (d, J=3.4 Hz, 1H, H_2), 3.78 (d, J=6.8 Hz, 1H, H_4), 3.31 (m, 1H, $H_{1'}$), 2.92 (m, 2H, H_5), 2.33 (d, J=10.4 Hz, 1H, NH), 2.25 (dd, J=14.2, 8.0 Hz, 1H, $H_{2'}$), 1.96 (dd, J=14.2, 5.6 Hz, 1H, $H_{2'}$), 1.23 (s, 9H).

3.6.2. Peptide elongation. Starting from a Met-Expansin® resin (300 mg, 0.216 mmol), Fmoc-Ahx-OH (252 mg, 0.71 mmol) was first introduced using the BOP reagent (288 mg, 0.65 mmol) and DIEA (0.169 mL, 0.99 mmol) in DMF. After removal of the Fmoc group with a solution of piperidine in DMF, thiazolidine **13a**, **b** (176 mg, 0.33 mmol) was introduced using the BOP reagent (144 mg, 0.33 mmol), HOBt (50 mg, 0.33 mmol) and DIEA (0.113 mL, 0.65 mmol). Deprotection of the trityl group was performed using a 1% TFA solution in MeOH and this cycle was repeated twice until the optical density of the filtrate was constant. All the other amino acids (3 equiv.) were introduced using the Fmoc strategy (Diisopropylcarbodiimide, 3 equiv., HOBt, 3 equiv., DIEA, 1.5 equiv.). Completion of the coupling steps was checked by the ninhydrin test of Kaiser.[24] After N-terminal acetylation, side chain protecting groups were removed by successive treatment with TFA/water (95:5). Cleavage from the resin followed our previously described procedure[7] leading to the caspase inhibitor Ac-Tyr-Val-Ala-Asp-H as a white powder. Yield: 54% (starting from **13a**, **b**). ^{1}H NMR ([D_4]MeOH) mixture of diastereoisomeric hemiacetals δ=7.04 (d, J=8.5 Hz, 2H, Tyr), 6.67 (d, J=8.5 Hz, 2H, Tyr), 4.55 (m, 2H, Asp), 4.33 (m, 1H, Tyr), 4.24 (m, 1H, Val), 4.13 (d, J=7.2 Hz, 1H, Ala), 3.01 (dd, J=14.0, 5.7 Hz, 1H, Tyr), 2.77 (dd, J=14.0, 9.3 Hz, 1H, Tyr), 2.69–2.60 (m, 1H, Asp), 2.52–2.45 (m, 1H, Asp), 2.05 (m, 1H, Val), 1.90 (s, 3H, Ac), 1.33 (d, J=7.2 Hz, 3H, Ala), 0.94 (d, J=6.6 Hz, 3H, Val), 0.92 (d, J=6.6 Hz, 3H, Val); MS (MALDI-TOF); m/z (%): 515 ($M+Na^+$), 537 ($M+2Na^+-1$). HPLC t_R=3.20 min using A/B 80:20 to A/B 50:50 in 10 min.

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