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Optically Active 4-Oxaproline Derivatives: New Useful Chiral Synthons Derived from Serine and Threonine.

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Abstract: A very simple procedure for the preparation of chiral optically active *N*-protected-4-carboxy-1,3-oxazolidine (4-oxaproline) derivatives starting from serine and threonine is described which avoids the use of toxic solvents or reagents. Elaboration of these compounds allows significant improvement in the handling of serine and threonine during the multigram preparation of oligopeptide structures and affords versatile chiral building blocks for the organic synthesis.

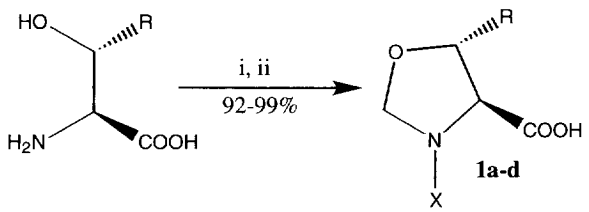
Recently, we have undertaken the synthesis of optically active 2-hydroxymethyl-[1] and 2-carboxy-5-alkylpiperazines,[2] with high enantiomeric excesses, as starting materials for 4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (CPP) analogs:[3] the reaction sequences we adopted were based on the preparation of dipeptides containing a serine unit. Following our interest in the synthesis of biologically active amino acids, it appeared necessary the development of a simple procedure for the preparation of a suitable Ser-Ser derivative in order to prepare 2,5-dicarboxy piperazine derivatives in large scale. To overcome the known interferences due to the unblocked hydroxy groups during the synthesis of peptides,[4] we have looked for a convenient and facile way to prepare *N*- and *O*-protected serine and threonine. Literature methods provide various orthogonally doubly protected intermediates, albeit prepared by roundabout routes.[5] An alternative is the simultaneous protection of hydroxy and amino group: the wide use of 2,2-dimethyl-*N*-(*tert*-butoxycarbonyl)-4-carboxymethyl-1,3-oxazolidine,[6,7] seemed to point out the great versatility of oxazolidine derivatives. In this field, a not recent report describes the possibility of converting DL-serine or threonine to 1,3-oxazolidine-4-carboxylic acid derivatives.[8] By these authors, serine (or threonine) and formaldehyde, in aqueous medium, are in equilibrium with 1,3-oxazolidine-4-carboxylate: at pH value greater than 7 the oxazolidine adduct can be "trapped" under Schotten-Baumann conditions leading to the corresponding *N*-benzoyl derivative.[8]

On this basis, we have developed some simple modifications to the published procedures which allow the recover of stable optically pure (*S*)-3-(benzyloxycarbonyl)-4-carboxy-1,3-oxazolidine (**1a**) and (4*S*,5*R*)-3-(benzyloxycarbonyl)-4-carboxy-1,3-oxazolidine (**1c**), in a one-pot reaction and in almost quantitative yields (Scheme 1).

In the same conditions, the treatment of the reaction mixtures with $(Boc)_2O$ afforded only small quantities (<30%) of (*S*)-3-(*tert*-butoxycarbonyl)-4-carboxy-1,3-oxazolidine (**1b**) or (4*S*,5*R*)-3-(*tert*-butoxycarbonyl)-4-

carboxy-5-methyl-1,3-oxazolidine (**1d**). In this case, the presence of catalytic amount of NH_2OH in the mixture achieved however efficient formation of compounds **1b** and **1d** (94÷95%).

Scheme 1

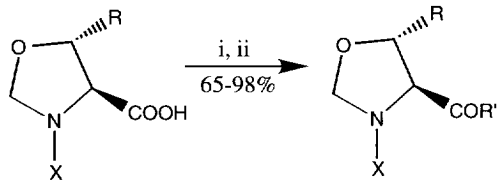


a, R = H, X = Cbz
b, R = H, X = Boc
c, R = Me, X = Cbz
d, R = Me, X = Boc

Reagents and conditions: i) HCHO, NaOH 2N, 0° C, 12 h. ii) Acetone, $(Boc)_2O$, NH_2OH cat., r.t., 3 h or Acetone, $NaHCO_3$, CbzCl, -4°C, 1h.

The easy recovering of *N*-protected 4-oxaproline derivatives **1a-d** in high yields prompted us to check their general applicability to organic synthesis: actually, this type of protection appears to be very suitable[6,7] for successive transformations of the carboxylic group without affecting the oxazolidine ring. For example, the treatment of compounds **1b** and **1d** with ethyl chloroformate and triethylamine in THF, followed by reaction with gaseous NH_3, furnished the amides **2e** and **2h** (95-98% yield, Scheme 2), whereas the treatment of **1b**-anhydride with anhydrous MeOH gave the ester **2d** (79%). By the same mixed anhydrides method, anilides **2a** and **2f** in high yields (88÷90%) were obtained too. Analogously, starting from derivatives **1a-b** and valine or serine methylester, we have prepared some protected dipeptides, such as *N*-[(*S*)-3'-(Benzyloxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-valine methylester (**2b**), *N*-[(*S*)-3'-(*tert*-butoxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-valine methylester (**2g**) and *N*-[(*S*)-3'-(Benzyloxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-serine methylester (**2c**, 65% yield after recrystallization), which represent useful intermediates in the synthesis of optically active piperazine ligands[1] and 2-carboxy-5-alkylpiperazines.[2] Compounds **2b** and **2g** were obtained in 95% and 74% yield, respectively, as analytically pure products without further purification.

Scheme 2



2a, R = H, R' = -NHPh
2b, R = H, R' = -Val-OMe } X = Cbz
2c, R = H, R' = -Ser-OMe

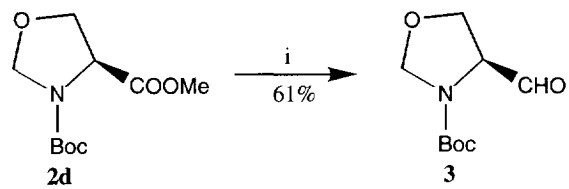
2d, R = H, R' = -OMe
2e, R = H, R' = $-NH_2$
2f, R = H, R' = -NHPh
2g, R = H, R' = -Val-OMe } X = Boc
2h, R = Me, R' = $-NH_2$

Reagents and conditions: i) EtOAc, NR_3, EtOCOCl, -15°C, 15 min. ii) Suitable amine or alcohol, r.t., 12.

In this context, it appeared interesting to check the possibility of obtaining *N*-protected 1,3-oxazolidine-4-formyl derivatives, that might be very important as a chiral, non racemic synthons in alternative to the well-known Garner aldehyde.[6,7] Thus, ester **2d** was reduced with diisobutylaluminum hydride at -80°C giving aldehyde **3** in 61% yield after distillative workup (Scheme 3).

The enantiomeric purity of compound **3** was controlled by oxidation of a sample to the acid **1b**: the comparison of the optical rotatory powers showed that no racemization occurred in the reductive process.

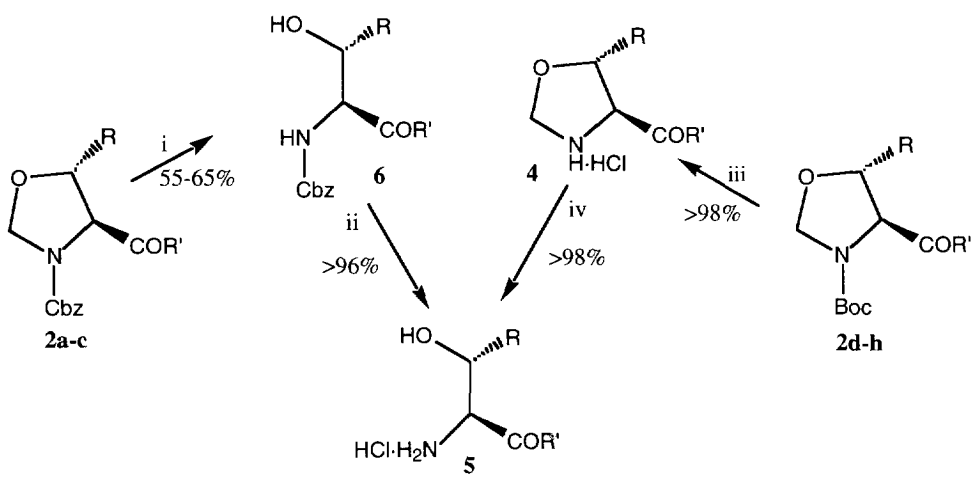
Scheme 3



Reagents and conditions: i) DIBAL, PhMe/hexane, -80°C, 2 h.

The selective removal of protecting groups is of critical importance in many synthetic sequences. Thus, we have checked the possibility of deblocking the oxazolidine derivatives **2a-h** to obtain different products under various experimental conditions: the results obtained (Scheme 4) have shown some efficient methods for the removal of the *N-O* methylene bridge or the *N*-Boc protecting group.

Scheme 4



Reagents and conditions: i) HCl 4N in MeOH, r. t., 12h. ii) MeOH, H_2, Pd/C 5%, HCl 1.1 eq., 2 h. iii) HCl 3N in EtOAc, r.t., 30 min. iv) MeOH, 65°C, 2 h.

The *N*-Boc-oxazolidines **2d-h** can be deprotected under smooth conditions affording the surprisingly stable 1,3-oxazolidine hydrochloride derivatives **4** in almost quantitative yield. In addition, compounds **4** can be further deprotected to afford the derivatives **5**.[9] On the other hand, the *N*-Cbz-oxazolidines **2a-c** can be cleaved leading to *N*-Cbz amides **6**, in 55-65% yields. The removal of the Cbz- group in compound **6** can be easily achieved by hydrogenolysis, affording hydrochlorides **5**.

The stability of the 1,3-oxazolidine ring is noteworthy: treatment of acid **1b** with HCl 3N in EtOAc afforded, in almost quantitative yield, 1,3-oxazolidine-4-carboxylic acid hydrochloride (4-oxaproline hydrochloride, **7**) as a stable, waxy solid.

The procedures adopted are very efficient for preparing functionalized derivatives containing 4-oxaproline mojety: moreover it appears possible to prepare either serinal or threoninal derivatives not *N*-Boc protected and therefore having an alternative use with respect to the serinal and threoninal acetonides.[6,7] Further experimental data have showed that compounds **5** are suitable for the incorporation of the 4-oxaproline ring in a oligopeptide structure, the nitrogen atom of oxazolidine ring being in fact able to form another peptide bond.[10]

In conclusion, we have shown that serine and threonine may be conveniently transformed in oxazolidine derivatives **1a-d** by one-pot procedure on multigram scale. The preliminary data reported show some of the synthetic potentialities of compounds **1a-d** in the oligopeptide synthesis, where the 4-oxaproline derivatives here described can be regarded as protected β-hydroxy α-amino acids or proline oxygenate isologs or conformationally constrained serine and threonine analogs: the method here reported offers a simple pathway to the synthesis of compounds containing these unnatural amino acids. In addition, these compounds (as well as their enantiomers) appear well suited as important chiral, not racemic synthons for the asymmetric synthesis of a large variety of nitrogen-containing targets: work is now in progress to investigate further on this field.[11]

Experimental section

Boiling points are uncorrected. Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Melting points were determined on a microscope Leitz LABORLUX S equipped with Leitz Microscope Heating Stage 350 and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 420 B analyser. All new compounds showed satisfactory microanalyses (within ± 0.3%). Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. GC analyses of the reaction products were carried out on a Perkin-Elmer 8600 gas chromatograph on fused silica megabore column (15 m x 0.53 mm) DB-1 or DB-5 (J&W), operating temperature programme (100-300°C, 5°C/min) and with an He flow rate of 9 mL/min. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions with TMS as internal standard or on D_2O solutions with deuterated sodium 3-(trimethylsilyl)propionate as internal standard. All reactions involving air sensitive materials were carried out under argon atmosphere: all reagents and solvents employed were reagent grade matherials purified by standard methods and distilled before use. As chiral starting materials, L-valine, L-serine and L-threonine (enantiomeric purity >99%) purchased from Janssen Chimica were used. H-Ser-OMe·HCl {mp 162-165°C, $[\alpha]_D^{25}$ -4.90 (*c* 1, MeOH)} and H-Val-OMe·HCl {mp 168-170°C, $[\alpha]_D^{21}$ +15.6 (*c* 2, H_2O)} were prepared as previously reported.[1]

(*S*)-3-(Benzyloxycarbonyl)-4-carboxy-1,3-oxazolidine, 1a - A solution of L-serine (31.5 g, 300 mmol) and formaldehyde (37%, 30 mL) in 2N NaOH (150 mL) was allowed to stand overnight at 0°C. After this time $NaHCO_3$ (25.2 g, 300 mmol) and acetone (150 mL) were added at 0°C. Then Cbz-Cl (52.0 g, 305 mmol) was added dropwise at -4°C, under vigorous stirring; the reaction mixture, after 1h, was diluted with water, extracted with ether and the ether extracts were discarded. Ether extraction of acidified (3N HCl) aqueous phase, drying with

Na_2SO_4 and evaporation of the solvent afforded the pure (TLC, CH_2Cl_2/EtOAc = 50/50) compound **1a** (69.3 g, 92%) as a solid having m. p. 79-83°C; $[\alpha]_D^{25}$ -94.2 (*c* 1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ (ppm): 10.15-10.05 (bs, 1H), 7.40-7.30 (m, 5H), 5.22-5.14 (m, 2H), 5.09-4.95 (m, 2H), 4.60-4.46 (m, 1H), 4.29-4.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 174.1 (broad), 153.6 (broad), 135.7; 128.5, 128.2, 127.9, 79.3 (broad), 70.1 (broad), 67.8, 57.0. Calculated for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.32; H, 5.24; N, 5.59.

(*S*)-3-(*tert*-Butoxycarbonyl)-4-carboxy-1,3-oxazolidine, 1b - A solution of L-serine (31.5 g, 300 mmol) and formaldehyde (37%, 30 mL) in 2N NaOH (150 mL) was allowed to stand overnight at 0°C. After this time NH_2OH·HCl (2.01 g, 30 mmol), NaOH (1.2 g, 30 mmol) in H_2O (25 mL), and acetone (175 mL) were added at 0°C. Then $(Boc)_2O$ (72.0 g, 330 mmol) was added, at r.t.; the reaction mixture, after 3h, was diluted with water, extracted with ether and the ether extracts were discarded. Ethyl acetate extraction of acidified (20% aq. citric acid) aqueous phase, drying with Na_2SO_4 and evaporation of the solvent afforded the pure (TLC, CH_2Cl_2/EtOAc = 50/50) compound **1b** (61.5 g, 94%) as colorless oil that slowly crystallized on standing to a waxy solid. $[\alpha]_D^{25}$ = -81.8 (*c* 2.6, $CHCl_3$).^1H NMR ($CDCl_3$) δ (ppm): 7.80-8.10 (bs, 1H), 4.85-5.00 (m, 2H), 4.45 (bs, 1H), 4.20 (bs, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm): (mixture of two conformers) 175.2, 173.9, 153.5, 152.0, 82.0, 81.5, 79.4, 70.9, 70.0, 56.7, 28.2.Calculated for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.73; H, 6.93; N 6.47.

(4*S*, 5*R*)-3-(Benzyloxycarbonyl)-4-carboxy-5-methyl-1,3-oxazolidine, 1c - This product was prepared starting from L-threonine and following the same procedure described for the preparation of **1a**. For **1c** was found: 99% yield, colorless oil (TLC, CH_2Cl_2/EtOAc = 50/50), $[\alpha]_D^{25}$ -99.2 (*c* 1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ (ppm): 9.08 (bs 1H), 7.41-7.22 (m, 5H), 5.30-5.10 (m, 3H), 4.87 (bs, 1H), 4.33-4.21 (m, 1H), 4.09-3.96 (m, 1H), 1.73 (d, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): (mixture of two conformers) 174.9, 173.9, 153.7, 152.8, 135.6, 128.5, 128.1, 127.7, 79.6, 79.2, 78.6, 78.4, 67.9, 67.5, 63.3, 18.4. Calculated for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.7; N, 5.28. Found: C, 58.79; H, 5.9; N, 5.28.

(4*S*, 5*R*)-3-(*tert*-Butoxycarbonyl)-4-carboxy-5-methyl-1,3-oxazolidine, 1d - This product was prepared starting from L-threonine and following the same procedure described for the preparation of **1b**. For **1d** was found: 95% yield, colorless oil (TLC, CH_2Cl_2/EtOAc = 50/50), $[\alpha]_D^{25}$ -110.2 (*c* 1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ (ppm): 9.20 (bs, 1H), 5.17-5.04 (m, 1H), 4.83-4.72 (m, 1H), 4.28-4.17 (m, 1H), 3.98-3.83 (m, 1H), 1.45 (d, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm): (mixture of two conformers) 175.1, 173.8, 153.4, 152.2, 81.9, 81.4, 79.3, 78.8, 78.3, 63.7, 63.1, 28.1, 18.4. Calculated for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.04; H, 7.35; N, 6.00.

(*S*)-3-(Benzyloxycarbonyl)-4-carboxyanilido-1,3-oxazolidine, 2a - A solution of compound **1a** (10.6 g, 42 mmol) in EtOAc (80 mL) was cooled to -15 °C and *N*-methylmorpholine (4.3 g, 4.7 mL, 42 mmol) was added; at the same temperature ethylchloroformate (4.55 g, 4.0 mL, 42 mmol) was slowly dropped in 10 min and after additional 20 min to the resulting mixture distilled aniline (4.0 g, 4.0 mL, 43 mmol) was dropwise added. After 2 h the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was treated with water (100 mL) and EtOAc (100 mL). The organic and aqueous layers were separated and the aqueous layers were extracted with EtOAc. The collected organic phases were washed with 5% aq HCl, sat. aq NaCl, 10% aq $NaHCO_3$ and sat. aq NaCl (50 mL each) in that order, and dryed (Na_2SO_4). The solvent was removed under reduced pressure affording pure (TLC, CH_2Cl_2/EtOAc = 50/50) **2a** (12.5 g, 90% yield) as a white solid having m. p. 115–116°C; $[\alpha]_D^{25}$ - 121.4 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 9.00-8.70 (bs, 1H), 7.50-7.41 (m, 1H), 7.40-7.25 (m, 8H), 7.14-7.05 (m, 1H), 5.26 (d, 1H, *J* = 4 Hz), 5.15 (d, 1H, *J* = 4 Hz), 5.10-5.03 (m, 1H), 4.95-4.87 (m, 1H), 4.58-4.50 (m, 1H), 4.52-4.40 (m, 1H), 4.20-4.09 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.4, 155.0 (broad), 137.2, 135.3, 128.9, 128.6, 128.5, 128.1, 124.5, 119.9, 79.7, 69.0 (broad), 68.1, 58.9. Calculated for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.37; H, 5.53; N, 8.55.

***N*-[(*S*)-3'-(Benzyloxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-valine methylester, 2b** - A solution of compound **1a** (10.6 g, 42 mmol) in EtOAc (80 mL) was cooled to -15 °C and *N*-methylmorpholine (4.3 g, 4.7 mL, 42 mmol) was added; at the same temperature ethylchloroformate (4.55 g, 4.0 mL, 42 mmol) was slowly

dropped in 10 min and after additional 20 min to the resulting mixture was added *N*-methylmorpholine (4.3 g, 4.7 mL, 42 mmol) and, portionwise, L-H-Val-OMe (7.0 g, 42 mmol). After 2 h the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was treated with water (100 mL) and EtOAc (100 mL). The organic and aqueous layers were separated and the aqueous layers were extracted with EtOAc. The collected organic phases were washed with 5% aq HCl, sat. aq NaCl, 10% aq $NaHCO_3$ and sat. aq NaCl (50 mL each) in that order, and dryed (Na_2SO_4). The solvent was removed under reduced pressure affording pure (TLC, CH_2Cl_2/EtOAc = 70/30) **2b** (14.6 g, 95%) as a colorless oil having $[\alpha]_D^{25}$ - 59.00 (*c* 0.6, $CHCl_3$); ^1H NMR, ($CDCl_3$) δ (ppm): 7.40-7.28 (m, 5H), 7.30-6.90 (bm, 1H), 5.21 (d, 1H, *J* = 4 Hz), 5.14 (d, 1H, *J* = 4 Hz), 5.10-5.00 (m, 1H), 4.89-4.82 (m, 1H), 4.53-4.40 (m, 2H), 4.42-4.20 (bm, 1H), 4.18-4.03 (m, 1H), 3.67 (s, 3H), 2.20-2.05 (m, 1H), 0.92-0.78 (m, 6H). ^{13}C NMR, ($CDCl_3$) δ (ppm): 171.7, 169.3, 154.2, 135.5, 128.5, 128.3, 128.0, 79.6, 69.5 (broad), 67.8, 58.3 (broad), 57.0, 52.0, 31.0, 18.8, 17.5. Calculated for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.44; H, 6.62; N, 7.65.

***N*-[(*S*)-3'-(Benzyloxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-serine methylester, 2c** - This product was prepared starting from **2a** and L-H-Ser-OMe·HCl and following the same procedure described for the preparation of **2b**. For **2c** was found: recrystallized from EtOAc/petroleum ether (TLC, CH_2Cl_2/EtOAc = 50/50), 63% yield, mp 137-138°C, $[\alpha]_D^{25}$ - 73.88 (*c* 0.4, MeOH); ^1H NMR, ($CDCl_3$) δ (ppm): 7.37-7.28 (m, 5H), 7.30-7.20 (m, 1H), 5.17 (d, 1H, *J* = 5 Hz), 5.10 (d, 1H, *J* = 5 Hz), 5.05-4.98 (m, 1H), 4.93-4.87 (m, 1H), 4.64-4.56 (m, 1H), 4.45-4.39 (m, 1H), 4.23-4.16 (m, 2H), 3.97-3.82 (m, 2H), 3.72 (s, 3H), 3.60-3.46 (bm, 1H). ^{13}C NMR, ($CDCl_3$) δ (ppm): 170.5, 169.9, 153.9, 135.6, 128.5, 128.3, 128.0, 79.7, 70.3 (broad), 67.9, 62.5, 58.4, 54.8, 52.7. Calculated for : $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95. Found: C, 54.50; H, 5.76; N, 7.92.

(*S*)-3-(*tert*-Butoxycarbonyl)-4-carboxymethyl-1,3-oxazolidine, 2d - A solution of compound **1b** (6.5 g, 30 mmol) in dry CH_2Cl_2 (80 mL) was cooled to -15 °C and *N*-methylmorpholine (3.03 g, 3.3 mL, 30 mmol) was added; at the same temperature ethylchloroformate (3.24 g, 2.85 mL, 30 mmol) was slowly dropped in 10 min and after additional 20 min to the resulting mixture was added, dropwise, dry methanol (50 mL). After 2 h the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was treated with water (100 mL) and EtOAc (100 mL). The organic and aqueous layers were separated and the aqueous layers were extracted with EtOAc. The collected organic phases were washed with 20% aq ciric acid, sat. aq NaCl, 10% aq $NaHCO_3$ and sat. aq NaCl (50 mL each) in that order, and dryed (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was bulb to bulb distilled affording pure (GLC) **2d** as a colorless oil (5.48 g, 79%) having b. p. 91-95°C/0.04 mBar; $[\alpha]_D^{25}$ - 73.94 (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 4.88-4.67 (m, 2H), 4.85-4.60 (m, 1H), 4.43-4.24 (m, 1H), 4.10-3.96 (m, 1H), 1.84 (s, 9H). ^{13}C NMR, ($CDCl_3$) δ (ppm): (mixture of two conformers) 170.9, 152.3, 80.9, 79.3, 71.0, 70.2, 57.3, 56.8, 52.3, 28.1. Calculated for : $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.84; H, 7.43; N, 6.09.

(*S*)-3-(*tert*-Butoxycarbonyl)-4-carbamoyl-1,3-oxazolidine, 2e - A solution of compound **1c** (30.1 g, 120 mmol) in dry THF (250 mL) was cooled to -20 °C and Et_3N (12.2 g, 16.9 mL, 121mmol) was added during 20 min and kept stirring for an additional 10 min, at the same temperature ethylchloroformate (13.1 g, 11.4 mL, 121 mmol) was slowly dropped in and after 20 min the resulting mixture, previously cooled at -30 °C, was saturated with ammonia gas and warmed to room temperature while stirring, for 20 hr. The reaction mixture was concentrated at reduced pressure (20 Torr) and the residue was diluted with water (100 mL) and extracted with EtOAc (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated affording pure (TLC, EtOH/Acetone = 70/30) **2e** as a colorless oil (28.5 g, 95%), $[\alpha]_D^{27}$ -83.7 (*c* 3.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 6.80-6.40 (bm, 1H), 5.71-5.55 (bm, 1H), 4.94-4.86 (m, 1H), 4.76-4.70 (m, 1H), 4.32-4.26 (m, 2H), 4.12-4.04 (m, 1H), 1.41 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.4, 153.3, 81.8, 79.6, 69.8 (broad), 58.1 (broad), 28.3. Calculated for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.95. Found: C, 49.90; H, 7.45; N, 12.99.

(*S*)-3-(*tert*-Butoxycarbonyl)-4-carboxyanilido-1,3-oxazolidine, 2f - This product was prepared starting from **1b** and following the same procedure described for the preparation of **2a** (20% aq citric acid was used instead of 3N

HCl). For **2f** was found: 88% yield (TLC, CH_2Cl_2/EtOAc = 85/15), m. p. 120°C (dec); $[\alpha]_D^{25}$ - 123.9 (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 9.30-8.80 (bs, 1H), 7.50 (d, 2H, *J* = 1 Hz), 7.28 (dd, 2H, J_1 = 1 Hz, J_2 = 0.7 Hz), 7.09 (t, 1H, *J* = 0.7 Hz), 5.05-4.94 (m, 1H), 4.88-4.77 (m, 1H), 4.57-4.36 (m, 2H), 4.21-4.07 (m, 1H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.8, 154.3 (broad), 137.5, 128.9, 124.4, 119.8, 82.3, 79.7, 69.2 (broad), 58.7 (broad), 28.2. Calculated for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.9; N, 9.58. Found: C, 61.69; H, 6.87; N, 9.55.

***N*-[(*S*)-3'-(*tert*-Butoxycarbonyl)-1',3'-oxazolidine-4'-carbonyl]-(*S*)-valine methylester, 2g** - This product was prepared starting from **1b** and following the same procedure described for the preparation of **2b** (20% aq citric acid was used instead of 3N HCl). For **2g** was found: colorless waxy solid (TLC, CH_2Cl_2/EtOAc = 85/15), 74% yield, $[\alpha]_D^{25}$ - 80.2 (*c* 1, $CHCl_3$); ^1H NMR, ($CDCl_3$) δ (ppm): 7.40-7.00 (bm, 1H), 5.00-4.89 (m, 1H), 4.80-4.72 (m, 1H), 4.52-4.43 (m, 1H), 4.39-4.31 (m, 1H), 4.13-4.02 (m, 1H), 3.69 (s, 3H), 2.22-2.04 (m, 1H), 1.45 (s, 9H), 0.91-0.81 (m, 6H). ^{13}C NMR, ($CDCl_3$) δ (ppm): 171.8, 169.8, 153.7, 81.9, 79.5, 69.1 (broad), 57.8 (broad), 56.9, 52.0, 31.1, 28.0, 18.9, 17.4. Calculated for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.62; H, 7.91; N, 8.51.

(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-carbamoyl-5-methyl-1,3-oxazolidine, 2h - This product was prepared starting from **1d** and following the same procedure described for the preparation of **2e**. For **2h** was found: oil (TLC, EtOH/Acetone = 70/30), 98% yield, $[\alpha]_D^{27}$ -98.9 (*c* 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 6.60-6.20 (bm, 2H), 5.20-5.00 (m, 1H), 4.30-4.10 (m, 1H), 3.82-3.75 (m, 2H), 1.37-1.49 (m, 3H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.5, 153.9, 81.7, 78.8, 64.6 (broad), 28.2, 18.5. Calculated for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.10; H, 7.91; N, 12.15.

(*S*)-3-(*tert*-Butoxycarbonyl)-4-formyl-1,3-oxazolidine, 3 - Ester **2d** (4.62g, 20 mmol) was dissolved in anhydrous toluene (10 mL), the solution cooled to -80°C and diisobutylaluminum hydride (1 M in hexane, 50 mL, 50 mmol) was added slowly. Stirring was prolonged for 2h before careful addition of methanol (12 mL) and warming to r. t.. The mixture was the poured into 250 mL of aqueous HCl 1N, cooled at 0°C, then the phases were separated, the aqueous layer extracted with EtOAc (300 mL), the combined organic extracts washed with water and dried (Na_2SO_4) and evaporated in vacuo. Fractional distillation of the colourless oil gave pure (GLC) aldehyde **3** (2.45 g, 61%) having b. p. 91-95°C/0.7 mm; $[\alpha]_D^{25}$ - 74.58 (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 9.65-9.51 (bm, 1H), 5.00-4.80 (m, 2H), 4.34-3.95 (m, 3H), 1.14 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 198.8, 162.5, 81.6, 79.6, 68.5 (broad), 62.7, 28.1. Calculated for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.65; H, 7.50; N, 7.00.

A sample of aldeyde **3** was oxidized with a cold (0°C) aqueous solution of $KMnO_4$ for 3h: extractive work-up gave (4*S*)-3-(*tert*-butoxycarbonyl)-4-carboxy-1,3-oxazolidine, **1b**, having $[\alpha]_D^{25}$ -81.8 (*c* 2.6, $CHCl_3$).

Selective deprotections - The following procedures described for compounds **4**, **5** and **6** are representative for the transformations depicted in the Scheme 4.

***N*-[(*S*)-1',3'-Oxazolidine-4'-carbonyl]-(*S*)-valine methylester hydrochloride, 4** - A sample of product **2g** (1.65 g, 5 mmol) was dissolved in 5 mL of EtOAc; to this solution 4.5N HCl in EtOAc (17 mL) was rapidly added under magnetical stirring: slowly a precipitate was formed. After 30 min the solvent was removed in vacuo (0.01 mBar) affording pure (TLC, EtOH/Acetone = 70/30) **4** (1.33 g, 100%) as a white solid having m. p. 120-121°C, $[\alpha]_D^{25}$ - 35.46 (*c* 0.3, MeOH); ^1H NMR, (D_2O) δ (ppm): 4.73 (s, 2H), 4.34-4.30 (m, 1H), 4.18-4.13 (m, 1H), 4.00-3.93 (m, 1H), 3.90-3.82 (m, 1H), 3.64 (s, 3H), 2.22-2.06 (m, 1H), 0.90-0.82 (m, 6H). ^{13}C NMR, (D_2O) δ (ppm): 173.7, 168.0, 81.9, 60.4, 58.8, 54.6, 53.0, 52.9, 30.2, 18.3, 17.4. Calculated for $C_{10}H_{19}N_2O_4Cl$: C, 45.03; H, 7.18; N, 10.5. Found: C, 44.96; H, 7.15; N, 10.9.

***N*-[(*S*)-Seryl]-(*S*)-valine methylester hydrochloride, 5**

A - A sample of hydrochloride **4** (2.66 g, 10 mmol) was dissolved in MeOH and refluxed for 2 h. The solvent was removed in vacuo (0.05 mBar) affording pure (TLC, EtOH/Acetone = 70/30) **5** (2.5 g, 99%) as a waxy solid having $[\alpha]_D^{25}$ - 13.93 (*c* 1, MeOH); ^1H NMR, (D_2O) δ (ppm): 4.38-4.32 (m, 1H), 4.21-4.15 (m, 1H), 4.04-3.95 (m, 1H), 3.95-3.86 (m, 1H), 3.73 (s, 3H), 2.27-2.10 (m, 1H), 1.00-0.81 (m, 6H). ^{13}C NMR, (D_2O) δ (ppm): 174.2,

168.6, 60.9, 59.3, 55.1, 53.4, 30.7, 18.8, 17.9. Calculated for $C_9H_{19}N_2O_4Cl$: C, 42.44; H, 7.52; N, 11.00. Found: C, 42.34; H, 7.50; N 11.04.

B - To a sample of the dipeptide **6** (1.76 g, 5 mmol) dissolved in MeOH (30 mL) 1N HCl in MeOH (5.5 mL) and 5% Pd activated charcoal (0.18 g) were added. The resulting mixture was treated with H_2 (1.5 atm) in a Parr hydrogenator at r.t. for 6 h, filtered on Celite 521 and any volatile product was removed in vacuo (0.05 mBar) affording pure **5** (1.2 g, 98%) having the same physical constants of the product obtained by way **A**.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-seryl]-(*S*)-valine methylester, 6** - A sample of oxazilidine **2b** (3.6 g, 10 mmol) was treated with 4N HCl in MeOH (20 mL); after 12 h the reaction mixture was poured in water (200 mL), neutralized with $NaHCO_3$ and extracted with EtOAc (2 x 80 mL). The combined organic extracts were washed with sat. aq NaCl, dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc = 85/15) affording unreacted **2b** (0.91 g, 25%) and pure **6** (2.1 g, 60%) as a waxy solid having $[\alpha]_D^{25}$ - 16.44 (*c* 1, $CHCl_3$); ^1H NMR, ($CDCl_3$) δ (ppm): 7.40-7.30 (m, 5H), 7.15-7.05 (m, 1H), 6.00-5.91 (m, 1H), 5.20-5.07 (m, 2H), 4.55-4.46 (m, 1H), 4.37-4.26 (m, 1H), 4.05-4.00 (m, 1H), 3.81-3.62 (m, 1H), 3.74 (s, 3H), 2.26-2.10 (m, 1H), 0.98-0.80 (m, 6H). ^{13}C NMR, ($CDCl_3$) δ (ppm): 172.2, 170.9, 156.4, 135.9, 128.3, 128.0, 127.8, 67.0, 62.6, 57.3, 55.5, 52.1, 30.6, 18.8, 17.5. Calculated for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 58.02; H, 6.84; N, 7.96.

(*S*)-1,3-Oxazolidine-4-carboxylic acid hydrocloride, 7 - This product was prepared starting from **1b** and following the same procedure described for the preparation of **4**. For **7** was found: waxy solid (TLC, EtOH/Acetone = 70/30), 99% yield, $[\alpha]_D^{25}$ - 7.33 (*c* 1.8, MeOH). ^1H NMR (D_2O) δ (ppm): 4.69 (dd, 2H, J = 0.75 Hz), 4.11 (dd, 1H, J_1 = 4.5 Hz, J_2 = 3.5 Hz), 4.00 (dd, 1H, J_1 = 13 Hz, J_2 = 4.5 Hz), 3.89 (dd, 1H, J_1 = 13 Hz, J_2 = 3.5 Hz). ^{13}C NMR, (D_2O) δ (ppm): 171.0, 82.6, 60.2, 55.5. Calculated for $C_4H_8NO_3Cl$: C, 31.29; H, 5.25; N, 9.12. Found: C, 31.26; H, 5.27; N, 9.14.

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