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Introduction of 4(*S*)-oxazolidineacetic acid, 2-oxo (D-Oxac) motif in a polypeptide chain: synthesis and conformational analysis

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A four step synthesis of 4(*S*)-oxazolidineacetic acid, 2-oxo benzyl ester (D-Oxac-OBn) from L-Asp-OH in 45% overall yield is reported. The formation of by-products is completely avoided, by microwave irradiation and by the use of caesium carbonate as base. Moreover the synthesis and IR and ^{1}H NMR conformational analysis of the tetramers Boc-L-Val-D-Oxac-L-Ala-OBn and Boc-L-Val-D-Oxac-Aib-L-Ala-OBn in solution is reported.

Introduction

The synthesis of conformationally constrained amino acids is an important tool for the preparation of oligomers that assume a well defined secondary structure, such as helices, sheets and turns.[1] The conformational preferences of these molecules are indeed strongly influenced by structural constraints present in the monomers, such as tetrasubstituted α-amino acids,[2] cyclic α- and β-amino acids.[3] Furthermore new polymeric backbones with specific folding propensities ('foldamers')[4] have been proposed as the first stage in facilitating the design of entirely synthetic systems with a tertiary structure.[5]

We have recently described the synthesis of oligomers of (4*S*,5*R*)-4-methyl 5-carboxybenzyloxazolidin-2-ones (L-Oxd)[6] and L-pyroglutamic acid (L-pGlu)[7] and we have demonstrated that these molecules fold in ordered structures characterized by a *semi*-extended helical conformation, analogous to polyproline II[8] and do not exhibit the amide *cis–trans* dynamic equilibrium typical of the related poly (L-Pro)$_n$ I ⇆ II helices.[8] This effect is due to the presence of an imidic bond which always adopts only the *trans* conformation, even in the dimer. A typical effect of this behaviour is that the H_α chemical shift of the amino acid nearby is strongly deshielded by the *N*-acyl derivative (Fig. 1). We have demonstrated that the anomalous chemical shift value is associated with the occurrence of a weak α–CH. . .O=C hydrogen bond.[7b]

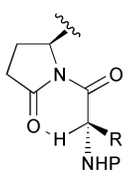


Fig. 1 The *trans* preferential conformation of the imido group is shown, with the α–CH. . .O=C hydrogen bond.

As a part of this project, we report here a straightforward synthesis of 4(*S*)-oxazolidineacetic acid, 2-oxo benzyl ester (D-Oxac-OBn) from L-aspartic acid (L-Asp-OH) (Fig. 2) and its introduction in small oligomers, in order to check if it favours the formation of a β-turn motif.[9]

Results and discussion

A couple of syntheses of 4(*S*)-oxazolidineacetic acid, 2-oxo (D-Oxac) derivatives have been described,[10] by hydrolysis or alcoholysis of (3*S*)-[(carbobenzyloxy)amino]-γ-butyrolactone,

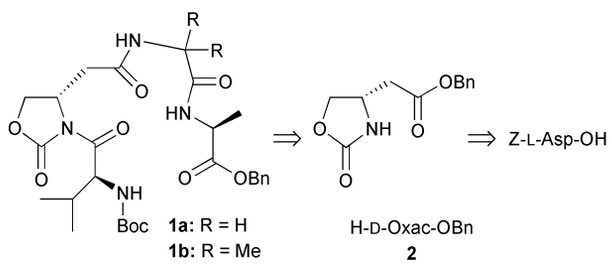
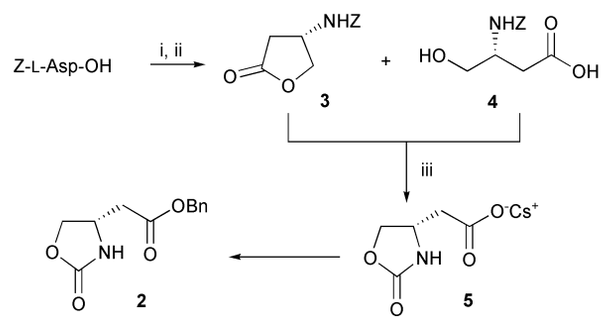


Fig. 2 Retrosynthesis of Boc-L-Val-D-Oxac-Gly-L-Ala-OBn **1a** and of Boc-L-Val-D-Oxac-Aib-L-Ala-OBn **1b** from Z-L-Asp-OH.

which in turn was prepared from Z-L-Asp-OH, using a known procedure.[11] For our purpose, we envisaged an efficient synthesis of the benzyl ester **2** by means of a four step preparation from Z-L-Asp-OH (Scheme 1).[12]



Scheme 1 *Reagents and conditions:* (i) Ac_2O (3 equiv.), microwave, 1 min; (ii) $NaBH_4$ (1.5 equiv.), dry THF, rt, 16 h; (iii) Cs_2CO_3 (3 equiv.), H_2O–acetone (3 : 1 ratio), 4 h, reflux; (iv) BnBr (1.5 equiv.), DMF, rt, 16 h.

By reaction with neat Ac_2O under microwave irradiation (210 W power, 1 min), Z-L-Asp-OH was transformed in the corresponding anhydride, which was reduced to the lactone **3** with $NaBH_4$ in dry THF. This reaction can afford a mixture of **3** and of the corresponding hydroxyacid **4**, so pure **3** or a mixture of **3** and **4** was treated with Cs_2CO_3 (3 equiv.) in water and acetone (3 : 1 ratio) for 4 hours at reflux, to obtain the caesium carboxylate **5** in quantitative yield, with the formation of benzyl alcohol as a side product. The solvents were removed under reduced pressure, DMF and benzyl bromide were added and the mixture was stirred at room temperature overnight.[13] After flash chromatography H-D-Oxac-OBn **2** was obtained pure in 45% overall yield from Z-L-Asp-OH.[14]

To check whether 4(*S*)-oxazolidineacetic acid, 2-oxo benzyl ester **2** (H-D-Oxac-OBn) favours the formation of a β-turn conformation, it was introduced into a short oligomer at the $i + 1$ position, which is commonly filled by proline[15] (Scheme 2). First, **2** was treated with Boc-L-Val-OPfp (Pfp = pentafluorophenyl) in the presence of *N*,*N*-dimethylaminopyridine (DMAP) and diisopropylethylamine (DIEA), to obtain Boc-L-Val-D-Oxac-OBn **6**, which was then hydrogenolysed to the corresponding acid **7**. The ^{1}H NMR spectra of both **6** and **7**

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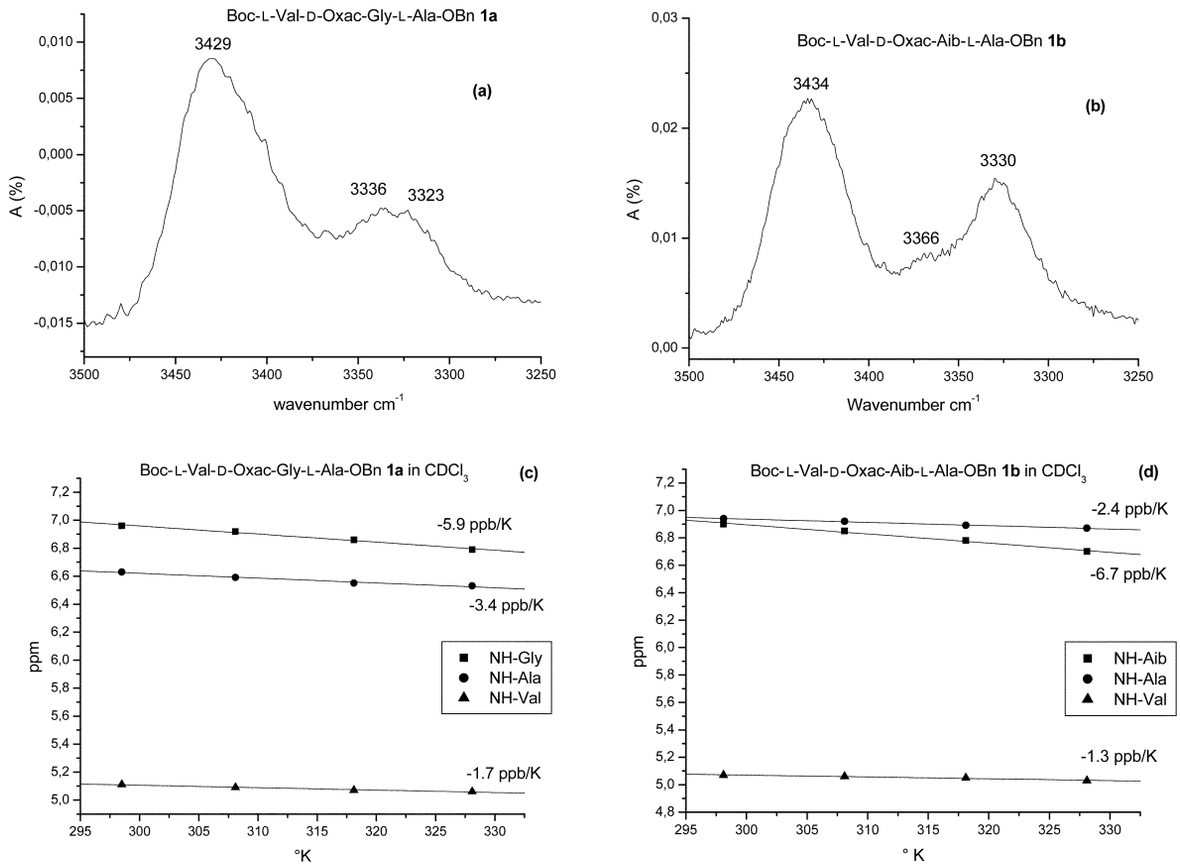
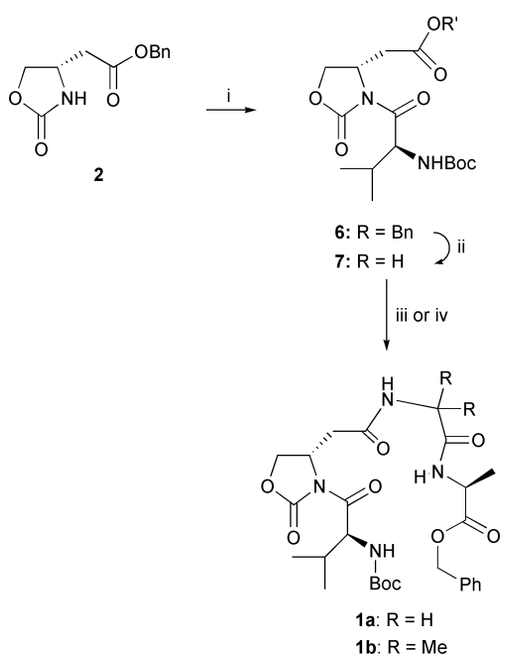


Fig. 3 (a) N–H stretch FT-IR data for the 3 mM sample of **1a** in CH_2Cl_2 at room temperature, after subtraction of the spectrum of pure CH_2Cl_2; (b) N–H stretch FT-IR data for the 3 mM sample of **1b** in CH_2Cl_2 at room temperature, after subtraction of the spectrum of pure CH_2Cl_2; (c) amide protons ^{1}H NMR chemical shift of **1a** in $CDCl_3$ as a function of the temperature; (d) amide protons ^{1}H NMR chemical shift of **1b** in $CDCl_3$ as a function of the temperature.



Scheme 2 *Reagents and conditions:* (i) Boc-L-Val-OPfp (1.5 equiv.), DIEA (2.5 equiv.), DMAP (1 equiv.), dry DMF, rt, 16 h; (ii) Pd/C 10% (0.1 equiv.), H_2 (3 atm), AcOEt, rt, 3 h; (iii) H-Gly-L-Ala-OBn (2 equiv.), NMM (4 equiv.), HOBt (1.2 equiv.), EDCI (1.2 equiv.), dry DMF, rt, 16 h; (iv) H-Aib-L-Ala-OBn (2 equiv.), NMM (4 equiv.), HOBt (1.2 equiv.), EDCI (1.2 equiv.), dry DMF, rt, 16 h.

show that the α-CH chemical shift of the valine residue is strongly deshielded by the *N*-acyl derivative (**6**: 5.40 ppm and **7**: 5.42 ppm). This outcome was previously observed for both our L-Oxd and L-pGlu oligomers and is evidence for the stable *anti* disposition of the two carbonyl groups of the *semi*-cyclic acylurethane system.

The oligomers Boc-L-Val-D-Oxac-Gly-L-Ala-OBn **1a** and Boc-L-Val-D-Oxac-Aib-L-Ala-OBn **1b** were prepared by liquid phase synthesis, introducing respectively glycine and 2-amino-isobutyric acid (Aib)[16] at the $i + 2$ position. The coupling was performed with H-Gly-L-Ala-OBn and H-Aib-L-Ala-OBn[17] to yield the desired tetramers **1a** and **1b**, in good yield after silica gel chromatography.[18]

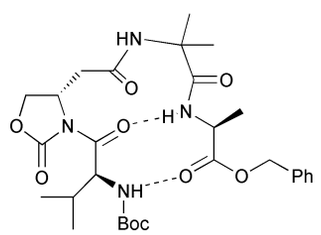
The preferential conformations assumed by **1a** and**1b** in solution of structure supporting solvents were analysed by IR and ^{1}H NMR spectroscopy (Fig. 3). The ^{1}H NMR spectra of both **1a** and **1b** show that the α-CH chemical shift of the valine residue resonates at 5.35 and 5.30 ppm respectively, as we previously observed for Boc-L-Val-D-Oxac-OBn **6** and Boc-L-Val-D-Oxac-OH **7**, thus showing that the functionalisation of the carboxy group does not affect the *anti* disposition of the two carbonyls of the imido group.

The IR spectrum of **1a**[19](Fig. 3a) shows the presence of two peaks at 3429 and 3326 cm^{-1} which can be ascribed to a non-hydrogen bonded NH amide proton and an hydrogen bonded NH amide proton respectively. The band at 3326 cm^{-1} is weak, so possibly an equilibrium between an open form and a turn is going on. The IR spectrum of **1b** (Fig. 3b) reports more encouraging results: two comparable bands at 3434 and 3330 cm^{-1} are present. More information on the conformational behaviour of our tetramers were obtained with the examination of the chemical shift dependence of the amide NH protons on the temperature in $CDCl_3$ (Figs. 3c–d). This test points out the presence of hydrogen-bonded amide protons: a small temperature coefficient (≤3 ppb K^{-1} in absolute value) indicates the presence of an hydrogen-bonded amide proton, while protons

which participate to an equilibrium between hydrogen-bonded and non hydrogen-bonded state show a larger temperature coefficient.[20] Following these criteria, only NH-Val of **1a** is hydrogen-bonded,[21] while in **1b** both NH-Val and NH-Ala are hydrogen-bonded amide protons.

This result is in full agreement with the IR spectra, which show a stronger band of hydrogen-bonded amide protons for **1b** than for **1a**, and it is quite reasonable, because the introduction of the Aib moiety as $i + 2$ amino acid enhances the rigidity of the whole system. NOESY experiments performed on the two samples (400 MHz, mixing time 900 ÷ 1,500 msec) furnish little additional information: **1a** shows a cross peak between NH-Ala and CH_2-Gly and another between α-CH-Ala and CH_2-Gly, besides the trivial ones. On the contrary, NOESY spectra of **1b** do not show any cross peak, besides the trivial ones.

All these data, when taken in conjunction, suggest that the preferential conformation of **1a** is somehow more extended and accommodates αCH hydrogens of Gly and Ala near to one another; while **1b** assumes a preferential β-turn conformation, with the chelation of NH-Val and NH-Ala (Fig. 4).



1b

Fig. 4 Preferential conformation assumed by **1b**, as it turns out from IR and ^{1}H NMR analysis.

In conclusion, we have shown a convenient and straightforward method for the synthesis of 4(*S*)-oxazolidineacetic acid, 2-oxo benzyl ester (D-Oxac-OBn) **2** from commercially available Z-L-Asp-OH. Furthermore, by IR and ^{1}H NMR analysis, we have tested its propensity to induce a β-turn conformation to the oligomers Boc-L-Val-D-Oxac-Gly-L-Ala-OBn **1a** and Boc-L-Val-D-Oxac-Aib-L-Ala-OBn **1b** in a solution of structure supporting solvents. This molecule is a promising scaffold for the design and synthesis of libraries of short oligomers with a well-defined secondary structure.

Acknowledgements

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14 D-Oxac-OBn **2** Mp = 82–83 °C; $[a]_D = -32.5$ (*c*. 1.0, CH_2Cl_2); IR: *v* 3240, 1731, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.64 (dd, 1 H, $J = 6.2$, 17.2 Hz, C*H*HCO), 2.74 (dd, 1 H, $J = 7.8$, 17.2 Hz, CH*H*CO), 4.05 (dd, 1 H, $J = 5.4$, 8.4 Hz, C*H*HO), 4.17–4.31 (m, 1 H, CHN), 4.55 (t, 1 H, $J = 8.4$ Hz, CH*H*O), 5.15 (s, 2 H, OCH_2Ph), 7.37 (s, 5 H, Ph); ^{13}C-NMR ($CDCl_3$) 39.7, 49.0, 67.2, 69.5, 128.7, 135.2, 159.0, 170.4.

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17 The dipeptides H-Gly-L-Ala-OBn and H-Aib-L-Ala-OBn were obtained in liquid phase, following the Boc-OBn protocol. The coupling agents are NMM, HOBt and EDCI.

18 **General method for the synthesis of 1a** and **1b**: To a stirred solution of **7** (0.25 mmol, 86 mg) in dry DMF (1 mL) was added H-Gly-L-Ala-OBn (0.5 mmol, 118 mg) or H-Aib-L-Ala-OBn (0.5 mmol, 130 mg), NMM (1 mmol, 0.11 mL), HOBt (0.3 mmol, 58 mg) and EDCI (0.3 mmol, 40 mg) under argon atmosphere. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate (20 mL) and washed with aqueous 1 N HCl (2 × 10 mL). The organic layer was dried over sodium sulfate, concentrated and the residue

was chromatographed (cyclohexane–ethyl acetate 7 : 3 as eluant). Boc-L-Val-D-Oxac-Gly-L-Ala-OBn **1a**: Yield 60%; low melting solid; $[\alpha]_D$ = +48.9 (*c.* = 0.9, CH_2Cl_2); IR (CH_2Cl_2): *ν* 3429, 3323, 1785, 1733, 1693 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 0.88 (d, 3 H, *J* = 6.6 Hz, Me), 1.04 (d, 3 H, *J* = 6.6 Hz, Me), 1.43 (s, 9 H, *t*-Bu), 1.68 (d, 3 H, *J* = 7.1 Hz, Me), 2.05–2.18 (m, 1H, C*H*Me_2), 2.68 (dd, 1 H, *J* = 8.7, 15.1 Hz, C*H*HCO), 2.84 (dd, 1 H, *J* = 2.3, 15.1 Hz, CH*H*CO), 3.93 (ABX, 2 H, *J* = 5.4, 5.7, 16.8 Hz, CH_2N), 4.40–4.52 (m, 2 H, CH_2O), 4.63 (dq *J* = 7.5 Hz, CHN), 4.74–4.84 (m, 1 H, CHN), 5.14 (br s, 1 H, NH), 5.17 (AB, 2 H, *J* = 12.3 Hz, OCH_2Ph), 5.29–5.38 (m, 1 H, CHN), 6.77 (br s, 1 H, NH), 7.07 (br s, 1 H, NH), 7.30–7.39 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$): *δ* 16.6, 18.2, 19.6, 28.3, 29.9, 37.8, 43.4, 48.3, 51.9, 57.6, 67.2, 80.4, 128.1, 128.4, 128.6, 135.3, 152.7, 156.2, 168.1, 169.5, 172.5, 173.3. Boc-L-Val-D-Oxac-Aib-L-Ala-OBn **1b**: Yield 65%; mp = 59–63 °C; $[\alpha]_D$ = +56.5 (*c.* = 0.2, CH_2Cl_2); IR (CH_2Cl_2): *ν* 3434, 3330, 1782, 1734, 1696, 1683 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 0.91 (d, 3 H, *J* = 7.0 Hz, Me), 1.06 (d, 3 H, *J* = 7.0 Hz, Me), 1.42 (d, 3 H, *J* = 7.0 Hz, Me), 1.44 (s, 9 H, *t*-Bu), 1.51 (s, 3 H, Me), 1.54 (s, 3 H, Me), 2.02–2.22 (m, 1 H, $CH(Me)_2$), 2.58–2.70 (m, 2 H, CH_2CO), 4.43 (dd, 1 H, *J* = 8.4, 9.2 Hz, C*H*HCO), 4.52–4.62 (m, 1 H, CHN), 4.61 (dd, 1 H, *J* = 7.2, 9.2 Hz, CH*H*CO), 4.72–4.86 (m, 1 H, CHN), 5.09 (d, 1 H, *J* = 8.0 Hz, NH), 5.17 (AB, 2 H, *J* = 12.2 Hz, O*CH*$_2$Ph), 5.30 (dd, 1 H, *J* = 4.8, 8.0 Hz, CHN), 6.90 (br s, 2 H, NH + NH), 7.25–7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$): *δ* 17.0, 18.4, 19.9, 25.0, 25.6, 28.6, 30.0, 38.6, 48.6, 52.1, 57.8, 67.3, 67.8, 80.7, 128.4, 128.8, 135.3, 150.2, 153.2, 169.0, 173.5, 173.8, 182.3.

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