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Oxazolidin-2-one-Containing Pseudopeptides That Fold into β-Bend Ribbon Spirals

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Abstract: Three sets of oligomers containing the 4-carboxy-5-methyloxazolidin-2-one (Oxd) moiety have been synthesized with the aim of checking whether these molecules are able to fold in ordered structures: A set [Boc-(L-Ala-L-Oxd)$_n$-OR], B set [Boc-(L-Ala-D-Oxd)$_n$-OR], and C set [Boc-(Aib-L-Oxd)$_n$-OR] preferential conformations have been analyzed with IR absorption, NMR, and CD. We have noticed that in these oligomers three stabilizing effects are active: (i) the rigid Oxd −CO−N(CH<)−CO− moiety, which always tend to assume a *trans* conformation; (ii) the formation of Oxd C═O···H−$^{\alpha}$C intramolecolar H-bonds; (iii) the alternate formation of 1 ← 4 intramolecular C═O···H−N H-bonds. Through the analysis of the experimental data, we could demonstrate that only the oligomers of the B set are able to meet all three requirements listed above. By a deeper insight into the CD spectra, we gathered that the secondary structure adopted by the B set oligomers is a β-bend ribbon spiral, which is a subtype of the 3_{10}-helix.

Introduction

Oligomers capable of folding into defined secondary structures ("foldamers") have recently received considerable attention.[1] Indeed, simplified artificial systems based on artificial backbones designed to fold in secondary structures may be used for the de novo design of molecules with interesting biological activities.[2]

Most unnatural foldamers reported so far have homogeneous backbones. Heterogeneous backbones, composed of two or more residue types, can also display well-defined folding behavior, although this strategy for foldamer design has received relatively little attention to date.[3]

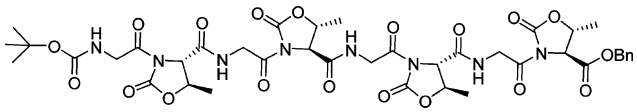

Figure 1. Chemical structure of Boc-(Gly-L-Oxd)$_4$-OBn (Boc = *tert*-butoxycarbonyl; OBn = benzyl).

The exploration of heterogeneous backbones is important because mixing monomer classes leads to an exponential increase in the range of potential foldamers. We have recently introduced some new oligomers, the basic unit of which was constructed by coupling a 4-carboxy-5-methyloxazolidin-2-one (Oxd) with Gly (Figure 1).[4]

Some Gly-L-Oxd oligomers up to the tetramer level were synthesized and their preferred conformations studied by means of IR absorption, ^{1}H NMR, and CD analyses. The combined results demonstrated a tendency to a preferential conformation, but the strong conformational freedom of the unsubstituted Gly residue somehow reduced the folding bias of the oligomers. Therefore, we decided to introduce a methyl group as a substituent for the Gly residue, thus utilizing L-Ala. Very likely, the methyl group should be introduced only on one face of the Gly methylene moiety, because only one side is expected to afford a stable secondary structure, while the other might contrast helix formation. Thus, oligomers of both the Boc-(L-Ala-L-Oxd)$_n$-OBn (L-Oxd = *trans*-(4*S*,5*R*)-4-carboxy-5-methyloxazolidin-2-one) and the Boc-(L-Ala-D-Oxd)$_n$-OBn (D-Oxd = *trans*-(4*R*,5*S*)-4-carboxy-5-methyloxazolidin-2-one) series were synthesized, to check whether the Gly *pro-S* hydrogen or the *pro-R* hydrogen should be replaced (Figure 2). Furthermore, some even more constrained oligomers of the Aib-L-Oxd series as well were synthesized and analyzed. Indeed, α-aminoisobu-

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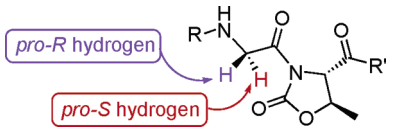
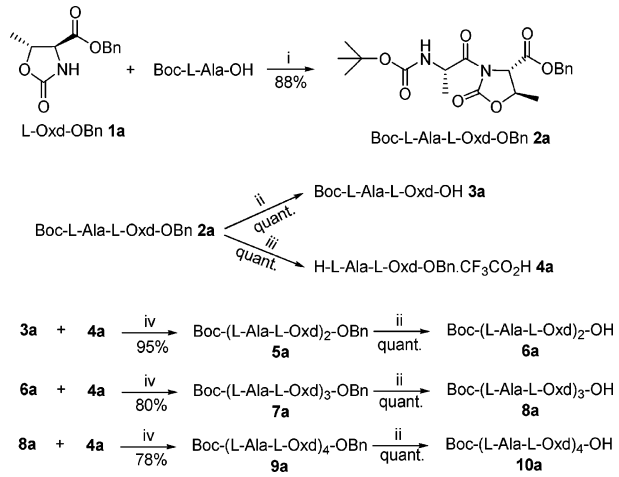


Figure 2. Chemical structure of the segment R-Gly-L-Oxd-R′. The *pro-R* and the *pro-S* α-hydrogens of the Gly residue are highlighted.

Scheme 1 [a]



[a] Reagents and conditions: (i) HBTU (1 equiv), DBU (1 equiv), dry CH_3CN, rt, 40 min; (ii) H_2, Pd/C (10%), MeOH, rt, 16 h; (iii) TFA (18 equiv), dry CH_2Cl_2, rt, 2 h; (iv) HATU (1.1 equiv), TEA (3 equiv), dry CH_3CN, 40 min, rt.

tyric acid (Aib) is a C^{α}-tetrasubstituted α-amino acid with two methyl groups that replace both the *pro-R* and the *pro-S* hydrogens.[5]

Results and Discussion

1. Synthesis. The pseudopeptide chains have been prepared in the liquid phase, starting from H-L-Oxd-OBn, H-D-Oxd-OBn, Boc-L-Ala-OH, and Boc-Aib-OH. While the latter two derivatives are commercially available, L-Oxd-OBn and its enantiomer were obtained in good yield by reaction of L- or D-threonine with triphosgene in the presence of NaOH: this is a well-known procedure which furnished the desired heterocycle in good yield. The benzyl group was introduced on the carboxy moiety, by reaction with benzyl bromide in the presence of triethylamine (TEA) or diisopropylethylamine (DIEA). Using this procedure, H-L-Oxd-OBn (**1a**) and H-D-Oxd-OBn (**1b**) were easily obtained in multigram scale.

First, we performed the synthesis of the oligomers of the Boc-(L-Ala-L-Oxd)$_n$-OR series (R = OBn, H) (Scheme 1). The dipeptide Boc-L-Ala-L-Oxd-OBn (**2a**) was obtained by coupling Boc-L-Ala-OH with **1a** in the presence of *N*-[(1*H*-benzotriazolyl)(dimethylamino)methylene]-*N*-methylmethaniminium hexafluorophosphate *N*-oxide (HBTU)[6] and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dry acetonitrile. It is crucial to perform the reaction under nitrogen, as the yield drastically falls in the presence of air. This effect should probably be ascribed

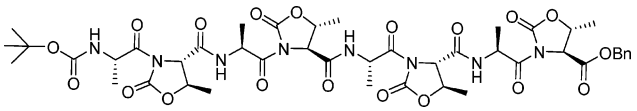


Figure 3. Chemical structure of Boc-(L-Ala-L-Oxd)$_4$-OBn (**9a**).

to the coupling reagents HBTU and DBU, which are very reactive and water sensitive. HBTU is an activated form of the classical 1-hydroxybenzotriazole (HOBt) and has been developed for the solid-phase synthesis of peptides. Recently, Carpino and co-workers[7] demonstrated that it can exist in two forms which are in equilibrium: the uronium form (more active) and the guanidinium form (less active). As the presence of DBU strongly favors the guanidinium form, it is essential to add the tertiary base always *after* the two reagents and *after* HBTU for the formation of the imide bond.

The L-Ala-L-Oxd oligomers up to the tetramer level were obtained by removal of the Boc N^{α}-protecting group by reaction with trifluoroacetic acid (TFA) in dry methylene chloride under a nitrogen atmosphere, which again is crucial to avoid decomposition of the resulting trifluoroacetate salt **4a**. The corresponding free amine, obtained by treatment of **4a** with a weak base ($NaHCO_3$), proved to be very unstable. Therefore, **4a** was coupled as such, utilizing one more equivalent of TEA during the coupling reaction.

Simultaneously, the OBn group was removed by reaction with H_2 in the presence of Pd/C (10%) in methanol to give the free acid **3a**. Both deprotections were complete in 2−3 h and afforded the desired compounds in quantitative yields.

The coupling reaction between **3a** and **4a** was performed by activation of **3a** with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)[8] and TEA in dry acetonitrile at room temperature under a nitrogen atmosphere as the reaction mixture is very sensitive to moisture. In this case, the coupling agent HBTU afforded unsatisfactory yields. The reaction was complete in 40 min, and Boc-(L-Ala-L-Oxd)$_2$-OBn (**5a**) was easily obtained in 95% yield, after flash chromatography using cyclohexane and ethyl acetate as eluants. The longer oligomers of the series, **7a** and **9a**, were obtained following the same procedure: hydrogenolysis of the ester moieties of **5a** and **7a** and coupling with **4a**.

Unfortunately, we could not prepare higher oligomers of the Boc-(L-Ala-L-Oxd)$_n$-OBn series, owing to the low solubility of both Boc-(L-Ala-L-Oxd)$_4$-OBn (**9a**) (Figure 3) and Boc-(L-Ala-L-Oxd)$_4$-OH (**10a**). This effect usually indicates that the compound has a high tendency to self-aggregate.

Then we prepared the oligomers of the Boc-(L-Ala-D-Oxd)$_n$-OBn series, starting from H-D-Oxd-OBn and Boc-L-Ala-OH (Scheme 2). We followed the same synthetic strategy used for the preparation of the Boc-(L-Ala-L-Oxd)$_n$-OBn series: each step was optimized and occurred with high to quantitative yield. In any case, the use of dry solvents and an inert atmosphere is crucial for high yield achievement.

Luckily, the compounds of this series proved to be more soluble in organic solvents, so that we could easily prepare Boc-(L-Ala-D-Oxd)$_6$-OBn (**13b**) (Figure 4) and the corresponding

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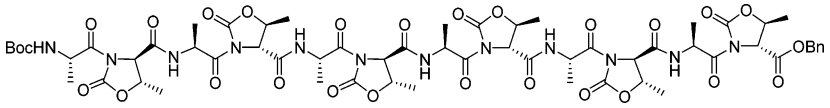
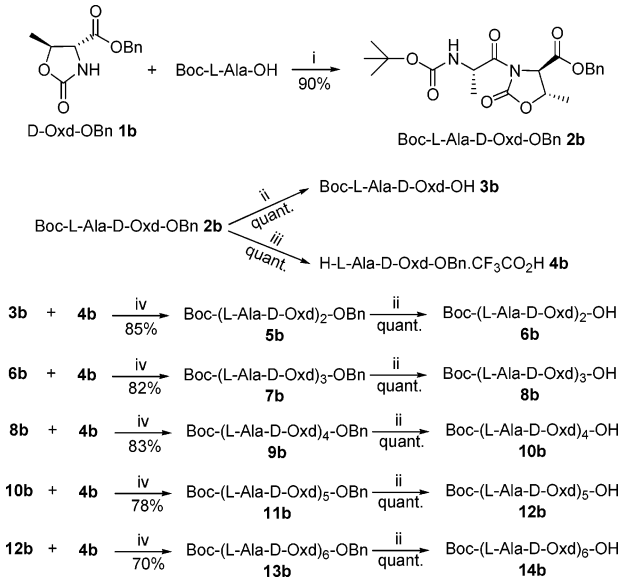


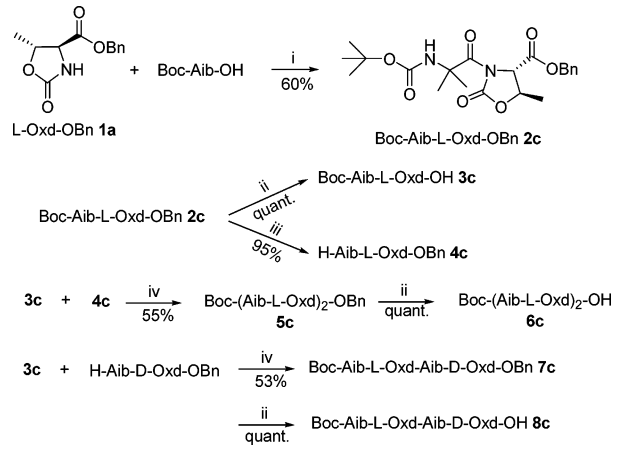
Figure 4. Chemical structure of Boc-(L-Ala-D-Oxd)$_6$-OBn (**13b**).

Scheme 2 [a]



[a] Reagents and conditions: (i) HBTU (1 equiv), DBU (1 equiv), dry CH_3CN, rt, 40 min; (ii) H_2, Pd/C (10%), MeOH, rt, 16 h; (iii) TFA (18 equiv), dry CH_2Cl_2, rt, 2 h; (iv) HATU (1.1 equiv), TEA (3 equiv), dry CH_3CN, 40 min, rt.

Scheme 3 [a]



[a] Reagents and conditions: (i) HBTU (1 equiv), DBU (1 equiv), dry CH_3CN, rt, 40 min; (ii) H_2, Pd/C (10%), MeOH, rt, 16 h; (iii) TFA (18 equiv), dry CH_2Cl_2, rt, 2 h; (iv) HATU (1.1 equiv), TEA (2 equiv), dry CH_3CN, 40 min, rt.

free acid Boc-(L-Ala-D-Oxd)$_6$-OH (**14b**). Surprisingly, the solubility of **13b** proved to be higher than that of the shorter **9b**.

The last series of oligomers described in this paper was obtained by coupling Boc-Aib-OH, **1a**, and **1b**. First, we prepared Boc-Aib-L-Oxd-OBn (**2c**), following the same reaction procedure described in Scheme 1. Then we selectively deprotected the carboxyl group by hydrogenolysis to form **3c** or the amino group by acid hydrolysis to form **4c**. The latter compound could be easily isolated as a free amine, being very stable even at room temperature (Scheme 3).

We could not obtain oligomers longer than Boc-(Aib-L-Oxd)$_2$-OBn (**5c**), owing to the low reactivity of the hindered Aib α-amino group. Boc-Aib-L-Oxd-Aib-D-Oxd-OBn (**7c**) was prepared to compare its properties with those of **5c**.

2. Conformational Analysis. Information on the preferred conformation of the described oligomers in solution was obtained in structure-supporting solvents (methylene chloride, deuteriochloroform, and methanol), by FT-IR absorption, ^{1}H NMR, and CD techniques. An additional interesting piece of information on the preferred crystal-state conformation was obtained by X-ray diffraction analysis of Boc-Aib-L-Oxd-OBn.

We analyzed three sets of oligomers: (i) A, Boc-(L-Ala-L-Oxd)$_n$-OR with $n = 1-4$ (R = Bn, H); (ii) B, Boc-(L-Ala-D-Oxd)$_n$-OR with $n = 1-6$ (R = Bn, H); (iii) C, Boc-(Aib-L-Oxd)$_n$-OR with $n = 1-2$ and Boc-Aib-L-Oxd-Aib-D-Oxd-OR (R = Bn, H).

The FT-IR absorption spectra of the three sets were obtained as 3 mM solutions in methylene chloride: at this concentration self-aggregation is usually unimportant. Only **9a** has been analyzed as a 0.5 mM solution, being not very soluble in methylene chloride.

Figure 5 shows the FT-IR absorption spectra (N−H stretching region) for all the synthesized compounds, and helps us to detect non-hydrogen-bonded amide N−H bands (above 3400 cm^{-1}) and hydrogen-bonded amide proton bands (below 3400 cm^{-1}). These results show that the three series behave in very different ways. Indeed, compounds of the A and the C sets (Figure 5a,c) show no propensity to form intramolecular C═O···H−N hydrogen bonds, while those of the B set (Figure 5b) form strong hydrogen bonds in oligomers longer than the trimer **7b**.

To further validate these results, the three sets of oligomers were analyzed by ^{1}H NMR spectroscopy. We have already demonstrated[9] that, in similar pseudopeptides, the formation of a C_{i+1}═O···H−C_i intramolecular H-bond can be spotted simply by checking the α-proton chemical shift, as the carbonyl proximity involves a marked deshielding of the proton chemical shift. In these series we observed this effect only in the L-Ala-containing sets A and B, because the Aib residues of set C have no α-hydrogens.

Table 1 lists the α-proton chemical shifts of all the Boc/OBn-protected pseudopeptides of the A and B sets, compared with that of Boc-L-Ala-OBn. A strictly comparable trend was observed for the C deprotected series (not shown). The chemical shift of the Boc-L-Ala-OBn α-hydrogen is reported in entry 1 and is at 4.4 ppm. In contrast, entries 2−11 show that the chemical shifts of the L-Ala moiety α-hydrogens of the benzyl esters of both the A and B sets are always deshielded by about 1 ppm, all resonating between 5.17 and 6.08 ppm.

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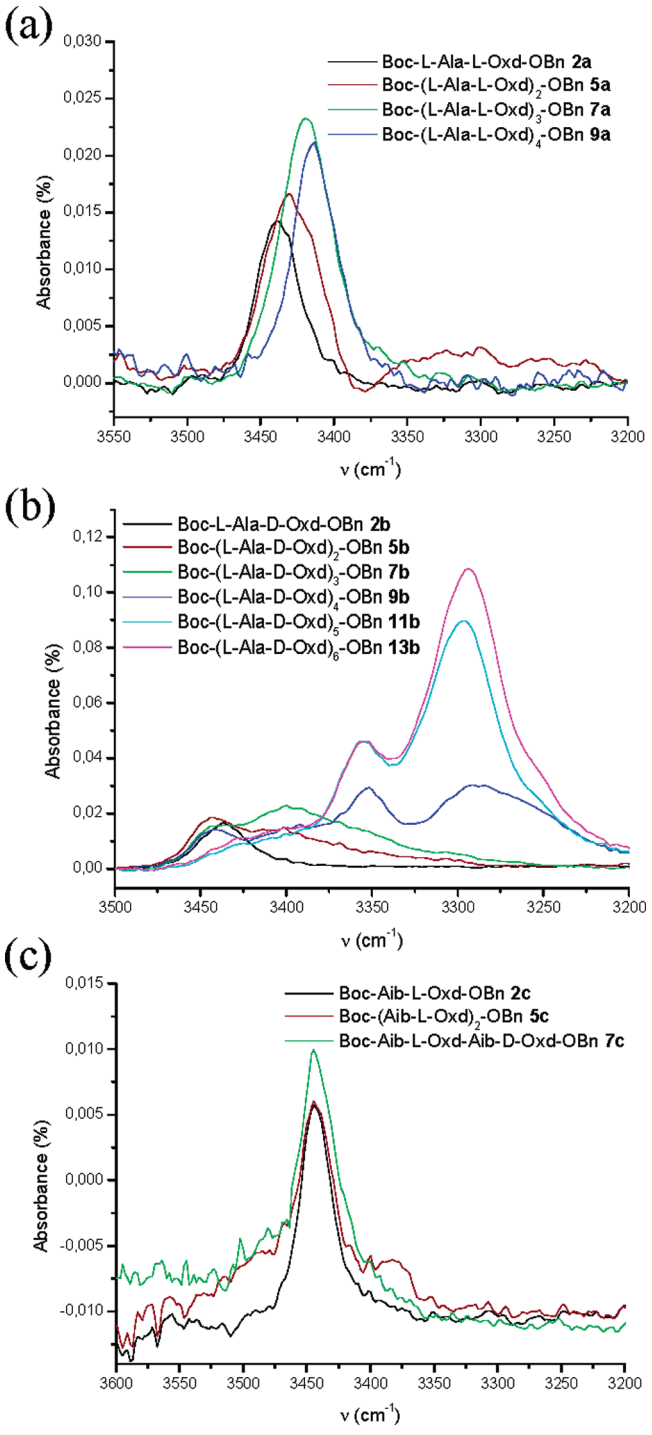

Figure 5. FT-IR absorption spectra in the N−H stretching region for 3 mM concentration samples of oligomers (a) **2a**, **5a**, **7a**, and **9a** in pure CH_2Cl_2 at room temperature (the concentration of **9a** is 0.5 mM, owing to its low solubility), (b) oligomers **2b**, **5b**, **7b**, **9b**, **11b**, and **13b**, and (c) oligomers **2c**, **5c**, and **7c**.

We ascribe this unusual chemical shift to the presence of an oxazolidin-2-one carbonyl in the vicinity of the α-CH proton of the L-Ala unit, in such a way that the imide −CO−N< bond external to the ring system is forced to accommodate the *trans* conformation. This conformation is stabilized by C═O···H−C intramolecular H-bonds. We have recently demonstrated by high-level DFT computational modeling on Boc-(L-pGlu)$_2$-OH (p-Glu, pyroglutamic acid) that this H-bond is responsible for

Table 1. α-Proton Chemical Shifts (ppm) for Boc-L-Ala-OBn and Pseudopeptides **2a**, **5a**, **7a**, **9a**, **2b**, **5b**, **7b**, **9b**, **11b**, and **13b** in 10^{-2} M Solutions in $CDCl_3$ at 25 °C

entry	compound	δ(α-CH)
1	Boc-L-Ala-OBn	4.40[a]
2	Boc-L-Ala-L-Oxd-OBn (**2a**)	5.35
3	Boc-(L-Ala-L-Oxd)$_2$-OBn (**5a**)	5.38, 5.60
4	Boc-(L-Ala-L-Oxd)$_3$-OBn (**7a**)	5.30, 5.42, 5.45
5	Boc-(L-Ala-L-Oxd)$_4$-OBn (**9a**)	5.25, 5.44 (2 H), 5.47[b]
6	Boc-L-Ala-D-Oxd-OBn (**2b**)	5.43
7	Boc-(L-Ala-D-Oxd)$_2$-OBn (**5b**)	5.28, 5.58
8	Boc-(L-Ala-D-Oxd)$_3$-OBn (**7b**)	5.17−5.46 (2 H), 5.48−5.58
9	Boc-(L-Ala-D-Oxd)$_4$-OBn (**9b**)	5.35−5.58 (4 H)
10	Boc-(L-Ala-D-Oxd)$_5$-OBn (**11b**)	5.18−5.50 (2 H), 5.83, 5.83, 6.07
11	Boc-(L-Ala-D-Oxd)$_6$-OBn (**13b**)	5.24−5.28, 5.60−5.67 (2 H), 5.75−5.98 (2 H), 5.98−6.08

[a] Reference 10. [b] This spectrum was recorded in CD_3OD, owing to the low solubility of compound **9a** in $CDCl_3$.

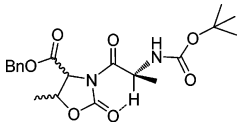

Figure 6. Preferred conformation for the pseudopeptide Boc-L-Ala-(L/D)-Oxd-OBn (**2a/b**). The preferential *trans* conformation of the imide moiety, which accounts for the anomalous chemical shift of the Ala Cα−H proton, is shown.

a stabilization of the *trans*-L-pGlu-L-pGlu conformation of about 1.4 kcal mol^{-1}.[9a]

This result is not surprising on energetic grounds as this imide conformation[11,12] is the one which allows the two nonbonded carbonyl oxygens of our *semi*cyclic system to be located the farthest apart (Figure 6).

Interestingly, in the present series the oligomers of both the A and B sets follow this trend, regardless of the absolute configurations of carbons 4 and 5 of the Oxd moiety, which on the contrary are crucial for the formation of intramolecular C═O···H−N hydrogen bonds, as deduced by IR absorption spectral analysis (Figure 5).

Although the oligomers of the C set do not contain α-protons able to form C═O···H−Cα H-bonds, the two nonbonded carbonyl oxygens of each semicyclic system are still located the farthest apart. This outcome was fully demonstrated by an X-ray diffraction analysis carried out on a single crystal of **2c**. The solid-state molecular structure of **2c** (Figure 7) revealed that the oxazolidinone and amidic (C10O4 and C9O3) carbonyls (Figure 7) point in opposite directions. Interestingly, in **2c** the Boc-NHC(CH$_3$)$_2$- chain adopts a conformation different from that found in *tert*-butyl *N*-(2-oxo-2-(4-isopropyl-2-oxo-5,5-diphenyloxazolidin-3-yl)ethyl) carbamate[13] (torsional angle O3C9C6N1 = 138.0(4)° in **2c** vs 5.8°) because of the two bulky methyl groups [C7, C8] replacing two hydrogens. No intramolecular C═O···H−N bond is formed between the endocyclic carbonyl and the NH of the Aib residue [dihedral angle between the O5C10N2O4 and N1C5O2O1 planes, 68.1(2)°] presumably because this would imply the formation of an unfavored seven-

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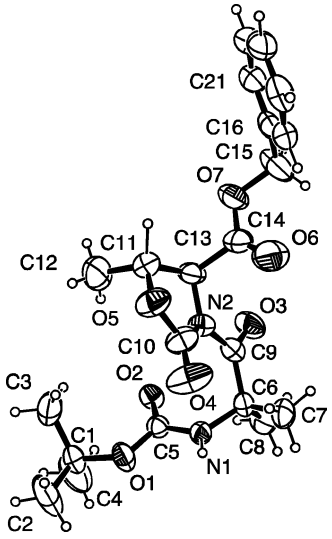

Figure 7. ORTEP drawing of Boc-Aib-L-Oxd-OBn (**2c**).

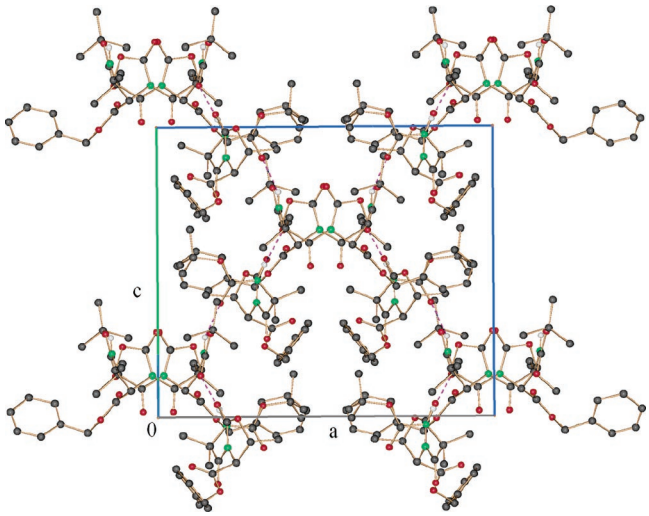

Figure 8. Crystal packing of **2c** showing the interpenetrating chains generated by intermolecular C═O···H—N hydrogen bonds running along the *c* axis.

membered ring. On the other hand, a closer examination of the crystal packing of the molecule (Figure 8) shows that intermolecular C═O···H—N bonds [N1—H10 = 0.91(6) Å, H10···O2′ = 2.19(6) Å, N1—H10···O2′ = 160(5)°] are formed. Moreover, the NH and CO groups being involved in hydrogen bonds on opposite sides, the molecules of **2c** generate interpenetrating *zigzag* chains running along the *c* axis. The conformational conclusions extracted from this X-ray diffraction study fit nicely with those obtained from our FT-IR absorption analysis discussed above.

The occurrence of intramolecular C═O···H—N H-bonds in oligomers of the A and B sets has been further detected by an investigation of the DMSO-d_6 dependence of NH proton chemical shifts.[14] This solvent is a strong hydrogen-bonding acceptor, and if it is bound to a free NH proton, it will be expected to dramatically move its chemical shift downfield. The results for the DMSO-d_6/$CDCl_3$ titrations of the NH protons of the pseudopeptides **7a**, **9b**, and **11b** are reported in Figure 9.

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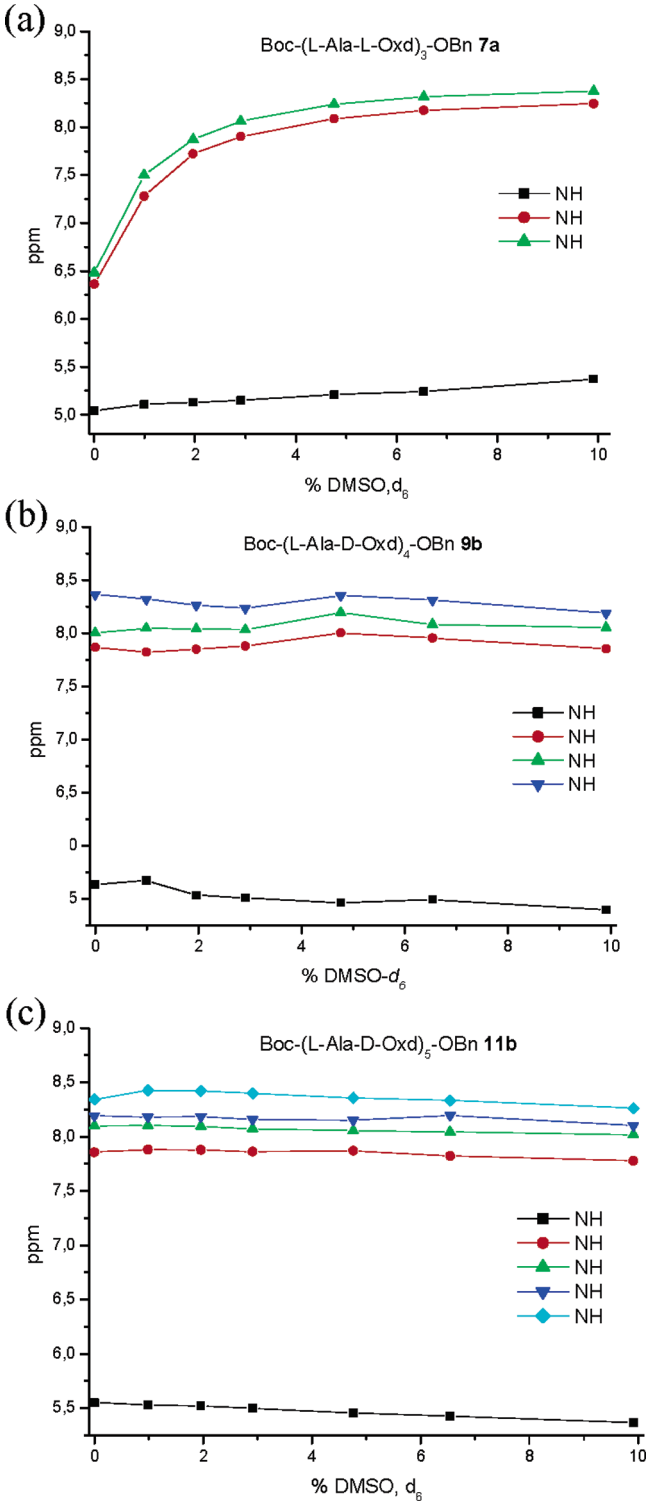

Figure 9. Variation of NH proton chemical shifts (ppm) of **7a** (a), **9b** (b), and **11b** (c) as a function of increasing percentages of DMSO-d_6 added to the $CDCl_3$ solution (v/v) (concentration 1 mM).

The outcome of these titrations is in perfect agreement with the results obtained using FT-IR absorption, as the NH protons of Boc-(L-Ala-L-Oxd)$_3$-OBn (**7a**) are very sensitive to DMSO while all of the NH protons of Boc-(L-Ala-D-Oxd)$_4$-OBn (**9b**) and Boc-(L-Ala-D-Oxd)$_5$-OBn (**11b**) are nearly insensitive to DMSO, thus confirming that **7a** is unable to form an H-bond-driven secondary structure while **9b** and **11b** are able to do so. Unfortunately, we were not able to titrate the longest oligomer

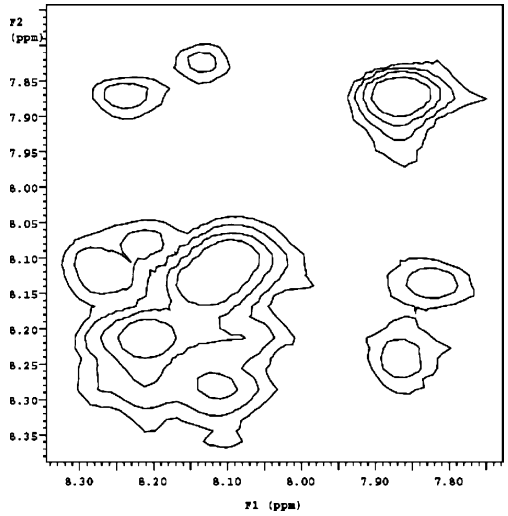

Figure 10. Significative NOE enhancements of **11b** obtained by performing the ROESY experiments on a 10 mM solution in $CDCl_3$ and utilizing a mixing time of 0.400 s.

of the A set, **9a**, under the same conditions owing to its poor solubility.

Another interesting piece of information has been obtained by ROESY experiments of a 10 mM solution of **11b** in $CDCl_3$ solution (Figure 10). From an inspection of the area between 7 and 9 ppm, many $N_iH \rightarrow N_{i+1}H$ cross-peaks, which usually account for the formation of a helix, are visible.[15]

Further confirmation of helix formation in the longer oligomers of the B set was obtained by recording the CD spectra of all free acids of the A−C sets in MeOH solution. Although this technique is intrinsically a low-resolution method,[16] it can furnish useful information on the presence of ordered secondary structures.[17] The per-residue CD spectra are reported in Figure 11.

The per-residue CD bonds of the A and C sets do no exhibit any significant change from the monomer to the higher oligomers, thus showing that no configurational effects (besides the absorption of the chromophore itself) take place. This result is at variance with that observed with the B set. The spectra of **3b**, **6b**, **8b**, and **10b** are nearly superimposable. On the contrary, an ellipticity increase, associated with a reversal of the Cotton effect, was observed for **12b** and more dramatically for **14b**. These CD spectra are indicative of an ordered secondary structure and agree well with the results obtained from the IR absorption and ^{1}H NMR analyses.

To define the nature of the ordered secondary structure formed by the pseudopeptides Boc-(L-Ala-D-Oxd)$_5$-OH (**12b**) and Boc-(L-Ala-D-Oxd)$_6$-OH (**14b**), we carefully analyzed their CD spectra in the absence of normalization (Figure 12).

The CD spectra of **12b** and **14b** (Figure 12a) display a negative CD band centered at about 207 nm followed by a negative shoulder at about 222 nm, while the ellipticity at 195 nm is positive. The shape of the CD spectrum of **14b** does not

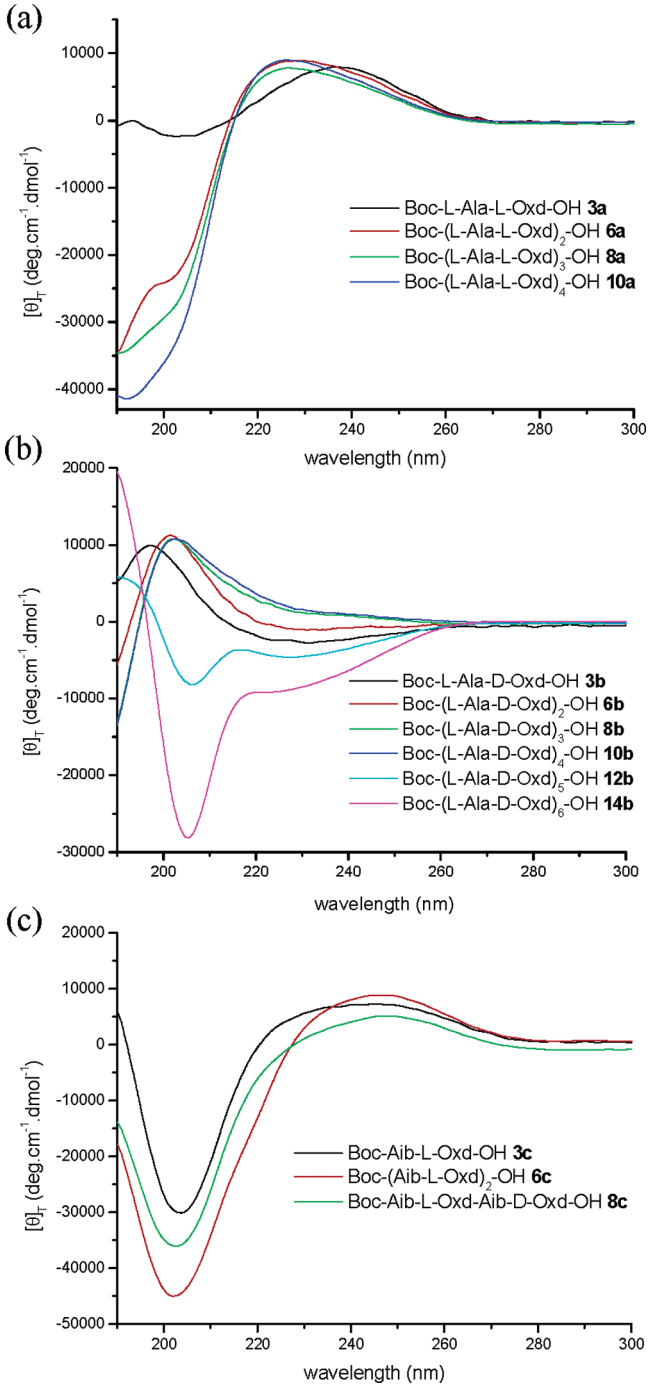

Figure 11. Normalized per-residue CD spectra of (a) Boc-(L-Ala-L-Oxd)$_n$-OH (n = 1−4) (**3a**, **6a**, **8a**, and **10a**), (b) Boc-(L-Ala-D-Oxd)$_n$-OH (n = 1−6) (**3b**, **6b**, **8b**, **10b, 12b,** and **14b**), and (c) **3c**, **6c**, and **8c** (1 mM concentration in MeOH solution).

change as the concentration decreases, as shown in Figure 12b, where the ellipticity of **14b** in MeOH solution at various concentrations is reported. This finding excludes formation of self-associated secondary structures.

Among the ordered peptide secondary structures which can be formed, we considered the CD spectra of the α- and 3_{10}-helices and the β-pleated sheet conformations. From a general inspection of the spectra shown in Figure 12, we deduce that **12b** and **14b** fold in the 3_{10}-helix. Indeed, Toniolo and co-workers[18] demonstrated that a 3_{10}-helix can be assigned by its CD spectrum, in agreement with the theoretical calculations.[19]

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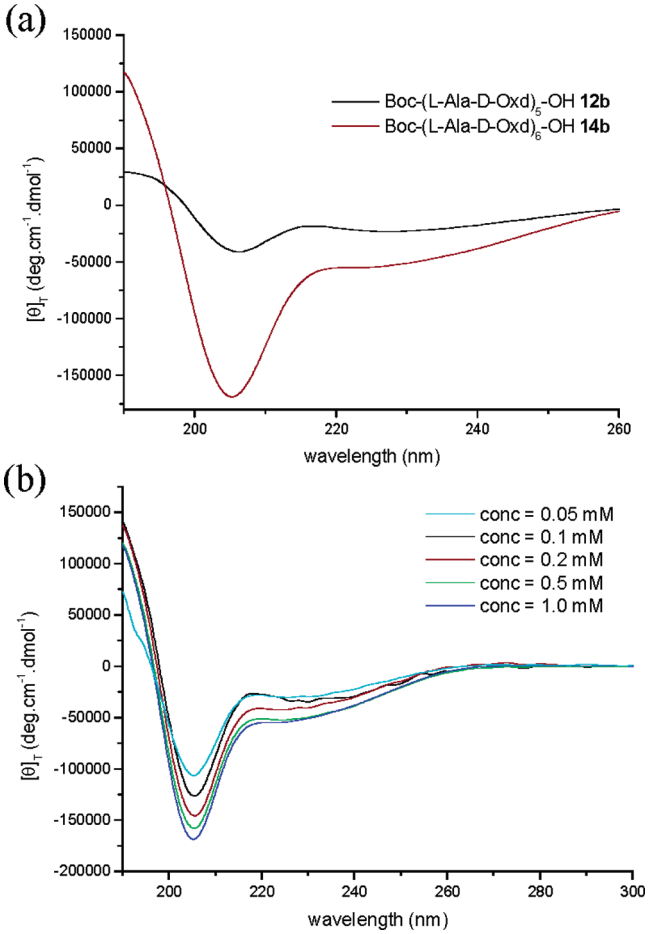

Figure 12. (a) CD spectra of Boc-(L-Ala-D-Oxd)$_5$-OH (**12b**) and Boc-(L-Ala-D-Oxd)$_6$-OH (**14b**) in MeOH solution (3 mM concentration). (b) CD spectra of **14b** at different concentrations in MeOH solution.

Table 2. Selected Molar Ellipticity Values for Boc-(L-Ala-D-Oxd)$_5$-OH (**12b**) and Boc-(L-Ala-D-Oxd)$_6$-OH (**14b**) in MeOH Solution at Different Concentrations at 25 °C

entry	compd	concn (mM, in MeOH)	$[\theta]_{195}\times10^{-3}$	$[\theta]_{207}\times10^{-3}$	$[\theta]_{222}\times10^{-3}$	$R=[\theta]_{222}/[\theta]_{207}$
1	**12b**	1	21.16	−40.59	−21.38	0.53
2	**14b**	1	35.59	−161.19	−55.09	0.34
4	**14b**	0.5	42.46	−151.82	−51.88	0.34
5	**14b**	0.2	59.79	−140.69	−42.02	0.30
6	**14b**	0.1	69.08	−121.14	−28.88	0.24
7	**14b**	0.05	15.5	−100.74	−29.33	0.29

Both theoretical and experimental studies point to the following main characteristics of the 3_{10}-helix: (a) a negative CD band centered near 207 nm; (b) a negative shoulder in the vicinity of 222 nm; (c) an $R = [\theta]_{222}/[\theta]_{207}$ ratio much weaker than the value reported for the α-helical peptides, which usually exhibit an R value of about 1; (d) a positive maximum at 198 nm.

Table 2 displays the most relevant ellipticity values for **12b** and **14b**.

Our experimental CD data meet all of the requirements for the 3_{10}-helix. More precisely, we can attribute to our oligomers

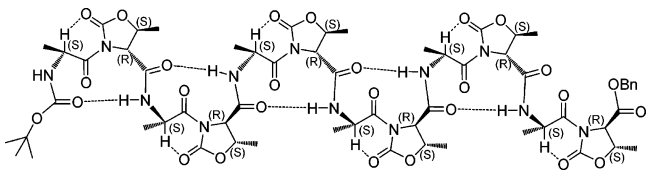

Figure 13. Conformation of Boc-(L-Ala-D-Oxd)$_6$−OBn (**13b**), where the three stabilizing effects are shown: (a) the rigid −CO−N(CH<)−CO− moiety, (b) the C═O···H−$^{\alpha}$C H-bonds, and (c) the C═O···H−N H-bonds.

12b and **14b** a β-bend ribbon spiral structure,[20] which may be considered a subtype of the polypeptide 3_{10} helix, being stabilized by alternate 1 ← 4 intramolecular C═O···H−N H-bonds and having approximately the same fold of the peptide chain. Indeed, Toniolo and co-workers[20b] reported the CD spectrum of (L-Pro-Aib)$_n$, which folds in a β-bend ribbon spiral structure. The spectrum is very similar to the CD spectrum reported in Figure 12.[21]

This outcome may be ascribed to the cooperative effect of many factors: (i) the rigid −CO−N(CH<)−CO− moiety, which always tends to assume a *trans* conformation; (ii) the formation of C═O···H−$^{\alpha}$C H-bonds; (iii) the alternate formation of C═O···H−N H-bonds. We believe that the combination of these three effects can hold the oligomers in a well-defined, rigid conformation (Figure 13).

Bearing these requirements in mind, we can understand why only oligomers of the B set form a β-bend ribbon spiral while the oligomers of the A set do not.

Figure 14 shows that only the oligomers of the B set are able to meet all three requirements listed above. Indeed, the rigid *trans* conformation of the −CO−N(CH<)−CO− moiety and the C═O···H−$^{\alpha}$C H-bond are present in both sets of pseudopeptides, so that the -L-Ala-L-Oxd- and -L-Ala-D-Oxd- sequences can be considered as rigid bicyclic moieties. As a result of this outcome, the side chains of the B set are *cis*, so that the carbonyls and the NH groups can form 1 ← 4 intramolecular C═O···H−N H-bonds. On the other hand, in the -L-Ala-L-Oxd- sequence, the two side chains are *trans*, so that a H-bond cannot be formed (Figure 14).

Conclusions

In this paper we reported the synthesis and conformational analysis of pseudopeptides containing alternate L-Ala or Aib residues and L-Oxd or D-Oxd residues. These pseudopeptides have been synthesized in the liquid phase, utilizing a uronium salt (HATU or HBTU) as the coupling agent under an inert atmosphere, which turned out to be crucial for good to excellent yields. The conformational analysis, performed in solution (IR absorption, ^{1}H NMR, ^{13}C NMR, CD) and in the crystal state

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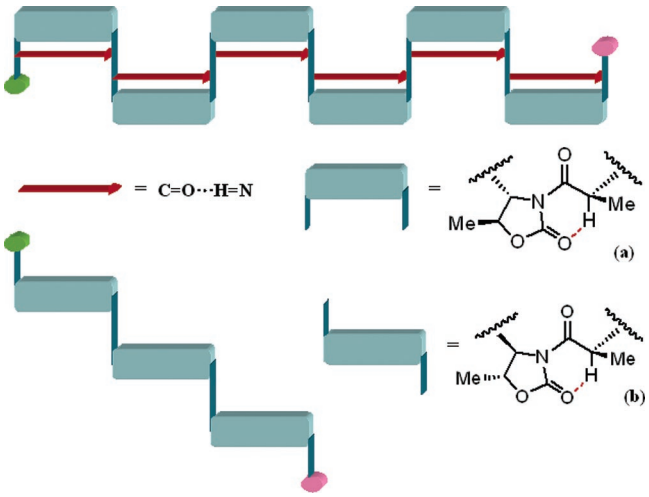

Figure 14. (a) A β-bend ribbon spiral formed by the Boc-(L-Ala-D-Oxd)$_n$-OR oligomers (B set) and (b) the impossibility to form an ordered secondary structure for the Boc-(L-Ala-L-Oxd)$_n$-OR oligomers (A set).

(X-ray diffraction), unambiguously proved that the oligomers having the general formula Boc-(L-Ala-D-Oxd)$_n$-OR ($n = 1-6$, R = Bn or H) fold in ordered structures with $n \geq 5$. With a deeper insight into the CD spectra, we could demonstrate that the secondary structure adopted is a β-bend ribbon spiral, which is a subtype of the 3_{10}-helix. Its formation should be ascribed to the cooperative effect of three factors: (i) the rigid Oxd −CO−N(CH<)−CO− moiety, which always tends to assume a *trans* conformation; (ii) the formation of Oxd C═O···H− $^{\alpha}$C intramolecolar H-bonds; (iii) the alternate formation of 1 ← 4 intramolecular C═O···H−N H-bonds, favored by the two side chains NHR and C(O)−NHR, both pointing in the same direction.

Experimental Section

Routine NMR spectra were recorded with spectrometers at 400, 300, or 200 MHz (^{1}H NMR) and at 100, 75, or 50 MHz (^{13}C NMR). Chemical shifts are reported in δ values relative to the solvent peak of $CHCl_3$, set at 7.27 ppm. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected.

High-quality infrared spectra (64 scans) were obtained at 2 cm^{-1} resolution using a 1 mm NaCl solution cell and a Nicolet 210 FT-infrared spectrometer. All spectra were obtained in 3 mM solutions in dry CH_2Cl_2 at 297 K. All compounds were dried in vacuo, and all the sample preparations were performed in a nitrogen atmosphere.

High-quality ^{1}H NMR spectra were recorded with a Varian Inova 600. Measurements were carried out in $CDCl_3$ and in DMSO-d_6 using tetramethylsilane as the internal standard. Proton signals were assigned by COSY spectra. Data for conformational analysis are obtained with 2D NOESY spectra with typical mixing times of 1.0 s.

The CD spectra were obtained on a Jasco J-810 spectropolarimeter. Cylindrical fused quartz cells of 0.02 cm path length were used. The values are expressed in terms of $[\theta]_T$, the total molar ellipticity (deg cm^2 dmol^{-1}).

Boc-L-Ala-L-Oxd-OBn (2a). To a stirred solution of Boc-L-Ala-OH (0.47 g, 2.5 mmol) in acetonitrile (20 mL) were added HBTU (0.98 g, 2.6 mmol), then L-Oxd-OBn (**1a**) (0.59 g, 2.5 mmol), and last DBU (0.75 mL, 5 mol). The mixture was stirred for 30 min, and then acetonitrile was removed under reduced pressure and was replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. Product **2a** was obtained pure in 88% yield (0.89 g) as a waxy solid after silica gel chromatography (cyclohexane/ethyl acetate, 9:1, as eluant): $[\alpha]_D$ −44.1 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3439, 1794, 1755, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 3H, J = 7.6 Hz), 1.42 (s, 9H), 1.51 (d, 3H, J = 6.4 Hz), 4.50−4.58 (m, 2H), 5.14 (br s, 1H), 5.17 (AB, 2H, J = 12.0 Hz), 5.35 (dq, 1H, J = 7.6 Hz), 7.25−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 20.9, 28.1, 48.8, 61.4, 67.9, 73.5, 79.7, 128.2, 128.4, 128.7, 134.3, 151.1, 154.9, 167.4, 173.9. Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.43): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.12; H, 6.50; N, 6.85.

Boc-L-Ala-L-Oxd-OH (3a). To a solution of Boc-L-Ala-L-Oxd-OBn (2 mmol, 0.81 g) in methanol (40 mL) was added 10% palladium on charcoal, and the mixture was stirred under a hydrogen atmosphere for 2 h. Then the catalyst was filtered on a Celite pad, and the mixture was concentrated. The corresponding acid Boc-L-Ala-L-Oxd-OH was obtained pure in quantitative yield without any further purification: mp 142 °C dec; $[\alpha]_D$ −25.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3437, 1792, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, 3H, J = 7.6 Hz), 1.43 (s, 9H), 1.56 (d, 3H, J = 6.2 Hz), 4.57 (d, 1H, J = 5.6 Hz), 4.68−4.75 (m, 1H), 5.27 (dq, 1H, J = 7.6 Hz), 6.75 (d, 1H, J = 7.6 Hz), 10.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 28.3, 50.2, 61.7, 73.9, 82.3, 151.6, 157.7, 170.6, 173.2. Anal. Calcd for $C_{14}H_{24}N_2O_7$ (332.35): C, 50.59; H, 7.28; N, 8.43. Found: C, 50.55; H, 7.20; N, 8.35.

H-L-Ala-L-Oxd-OBn·CF$_3$CO$_2$H (4a). A solution of **2a** (2 mmol, 0.83 g) and TFA (36 mmol, 2.78 mL) in dry methylene chloride (20 mL) was stirred for 4 h at room temperature, then the volatiles were removed under reduced pressure, and the product was obtained pure in quantitative yield without any further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H, J = 6.3 Hz), 1.65 (d, 3H, J = 5.6 Hz), 4.58−4.78 (m, 2H), 5.13−5.38 (m, 4H), 7.22−7.52 (m, 5H), 7.75 (br s, 3H).

Boc-(L-Ala-L-Oxd)$_2$-OBn (5a). To a stirred solution of **3a** (1 mmol, 0.33 g) and HATU (1 mmol, 0.38 g) in dry acetonitrile (10 mL) under an inert atmosphere was added a mixture of **4a** (1 mmol) and Et_3N (3 mmol, 0.44 mL) in dry acetonitrile (10 mL) at room temperature. The solution was stirred for 40 min under and inert atmosphere, and then acetonitrile was removed under reduced pressure and was replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 8:2, as eluant) in 95% yield: mp 128−131 °C; $[\alpha]_D$ −70.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3430, 1792, 1756, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42−1.46 (m, 15 H), 1.55 (d, 3 H, J = 5.6 Hz), 1.57 (d, 3H, J = 5.6 Hz), 4.37 (d, 1H, J = 4.4 Hz), 4.56 (d, 1H, J = 4.4 Hz), 4.60 (dq, 1H, J = 4.4, 5.6 Hz), 4.76 (dq, 1H, J = 5.6 Hz), 5.04 (d, 1H, J = 7.2 Hz), 5.21 (AB, 2H, J = 12.0 Hz), 5.38 (dq, 1H, J = 7.2 Hz), 5.60 (dq, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 7.30−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 18.1, 20.7, 21.1, 28.3, 48.5, 49.1, 61.4, 62.7, 68.2, 73.8, 74.1, 79.9, 128.4, 128.7, 128.9, 134.3, 151.1, 151.6, 155.1, 166.8, 167.4, 172.6, 174.7. Anal. Calcd for $C_{28}H_{36}N_4O_{11}$ (604.24): C, 55.62; H, 6.00; N, 9.27. Found: C, 55.67; H, 6.04; N, 9.23.

Boc-(L-Ala-L-Oxd)$_2$-OH (6a). For the synthetic procedure from **5a** see the above preparation of **3a**: quantitative yield; mp 116−119 °C dec; $[\alpha]_D$ −56.8 (*c* 1.0, CH_2Cl_2); IR (Nujol) ν = 3434, 3379, 1793, 1708 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 1.34 (d, 3H, J = 7.2 Hz), 1.42 (s, 9H), 1.46 (d, 3H, J = 7.2 Hz), 1.54 (d, 6H, J = 6.8 Hz), 4.53 (d, 1H, J = 4.4 Hz), 4.55 (d, 1H, J = 4.4 Hz), 4.72 (dq, 2H, J = 4.4, 6.8 Hz), 5.21 (q, 1H, J = 7.2 Hz), 5.43 (q, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.7, 17.3, 20.7, 21.2, 28.7, 49.7, 50.1, 62.7, 63.3, 75.9, 76.1, 80.6, 153.4, 153.8, 157.9, 170.2, 171.0, 174.0, 175.6. Anal. Calcd for $C_{21}H_{30}N_4O_{11}$ (514.19): C, 49.02; H, 5.88; N, 10.89. Found: C, 49.11; H, 5.83; N, 10.78.

Boc-(L-Ala-L-Oxd)$_3$-OBn (7a). For the synthetic procedure from **6a** and **4a** see the above preparation of **5a**: 80% yield; mp 187−189 °C

dec; $[\alpha]_D$ −143 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3418, 1791, 1754, 1701 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.39 (d, 3H, *J* = 7.2 Hz), 1.41 (d, 3H, *J* = 7.2 Hz), 1.47 (s, 9H), 1.48 (d, 3H, *J* = 7.2 Hz), 1.56 (d, 3H, *J* = 6.0 Hz), 1.59 (d, 3H, *J* = 6.0 Hz), 1.60 (d, 3H, *J* = 6.0 Hz), 4.56−4.63 (m, 4H), 4.69 (d, 1H, *J* = 4.4 Hz), 4.77 (dq, 1H, *J* = 4.4, 6.0 Hz), 5.21−5.30 (m, 3H), 5.42 (q, 1H, *J* = 7.2 Hz), 5.45 (q, 1H, *J* = 7.2 Hz), 7.30−7.41 (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.6, 16.7, 17.3, 20.6, 21.0, 49.6, 49.8, 50.1, 62.8, 63.2, 68.9, 80.6, 129.5, 129.6, 129.7, 136.4, 153.2, 153.7, 153.8, 157.9, 169.3, 170.0, 170.2, 173.9, 174.1, 175.5. Anal. Calcd for $C_{36}H_{46}N_6O_{15}$ (802.30): C, 53.86; H, 5.78; N, 10.47. Found: C, 53.92; H, 5.82; N, 10.52.

Boc-(L-Ala-L-Oxd)$_3$-OH (8a). For the synthetic procedure from **7a** see the above preparation of **3a**: quantitative yield; mp 173−174 °C dec; $[\alpha]_D$ −77.0 (*c* 1.0, CH_2Cl_2); IR (Nujol) ν = 3409, 1775, 1718, 1683 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.39 (d, 3H, *J* = 6.8 Hz), 1.46 (s, 9H), 1.49 (d, 3H, *J* = 7.2 Hz), 1.51 (d, 3H, *J* = 7.2 Hz), 1.56−1.61 (m, 9H), 4.53−4.64 (m, 5H), 4.77 (dq, 1H, *J* = 4.4, 6.4 Hz), 5.25 (q, 1H, *J* = 6.8 Hz), 5.44 (q, 1H, *J* = 7.2 Hz), 5.48 (q, 1H, *J* = 7.2 Hz); ^{13}C NMR (CD_3OD 100 MHz) δ 16.6, 17.2, 17.6, 20.6, 21.1, 21.2, 28.6, 49.5, 49.6, 50.1, 62.8, 63.2, 63.3, 76.0, 76.1, 76.3, 80.6, 153.5, 153.7, 153.9, 157.9, 170.0, 170.2, 171.2, 173.9, 174.1, 175.5. Anal. Calcd for $C_{29}H_{40}N_6O_{15}$ (712.26): C, 48.87; H, 5.66; N, 11.79. Found: C, 48.91; H, 5.71; N, 11.79.

Boc-(L-Ala-L-Oxd)$_4$-OBn (9a). For the synthetic procedure from **8a** and **4a** see the above preparation of **5a**: 78% yield; mp 210 °C dec; $[\alpha]_D$ −127.5 (*c* 1.0, MeOH); IR (CH_2Cl_2, 2 mM) ν = 3414, 1798, 1771, 1718, 1686, 1607 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.38 (d, 3H, *J* = 7.2 Hz), 1.41 (d, 3H, *J* = 6.8 Hz), 1.45−1.50 (m, 15H), 1.56 (d, 3H, *J* = 6.8 Hz), 1.59 (d, 9H, *J* = 6.0 Hz), 4.55−4.62 (m, 6H), 4.69 (d, 1H, *J* = 4.8 Hz), 4.77 (dq, 1H, *J* = 4.8, 6.4 Hz), 5.25 (AB, 2H, *J* = 12.4 Hz), 5.22−5.28 (m, 1H), 5.44 (q, 2H, *J* = 7.2 Hz), 5.47 (q, 1H, *J* = 6.8 Hz), 7.35−7.41 (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.6, 16.7, 17.3 (two signals), 20.6 (three signals), 21.0, 28.6, 49.5, 49.6, 49.9, 50.1, 62.8, 63.1, 63.2, 63.5, 69.0, 74.8, 75.5, 76.1, 76.3, 80.7, 129.4, 129.5, 129.6, 136.4, 153.2, 153.7, 157.8, 157.9, 169.3, 169.9, 170.0, 170.2, 173.9, 174.0, 174.1, 175.5. Anal. Calcd for $C_{44}H_{56}N_8O_{19}$ (1000.37): C, 52.80; H, 5.64; N, 11.19. Found: C, 52.89; H, 5.57; N, 11.21.

Boc-(L-Ala-L-Oxd)$_4$-OH (10a). For the synthetic procedure from **9a** see the above preparation of **3a**: quantitative yield; mp 188−192 °C dec; $[\alpha]_D$ −118.0 (*c* 1.0, MeOH); IR (Nujol) ν = 3412, 1792, 1769, 1721, 1685 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.38 (d, 3H, *J* = 6.8 Hz), 1.47 (s, 9H), 1.49 (d, 9H, *J* = 7.2 Hz), 1.57−1.61 (m, 12H), 4.55 (d, 1H, *J* = 4.0 Hz), 4.56−4.63 (m, 6H), 4.76 (dq, 1H, *J* = 4.4, 6.4 Hz), 5.25 (q, 1H, *J* = 7.2 Hz), 5.41−5.52 (m, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.5, 16.6, 16.7, 17.3, 20.6 (three signals), 21.2, 28.6, 49.4, 49.6, 49.7, 50.1, 63.1 (two signals), 63.2, 63.3, 76.1 (two signals), 76.3 (two signals), 80.7, 153.6, 153.8, 153.9, 157.9, 170.0, 170.1, 170.2, 171.5, 173.9, 174.0, 174.1, 175.5. Anal. Calcd for $C_{37}H_{50}N_8O_{19}$ (910.32): C, 48.79; H, 5.53; N, 12.30. Found: C, 48.75; H, 5.57; N, 12.33.

Boc-L-Ala-D-Oxd-OBn (2b). For the synthetic procedure from **1a** see the above preparation of **2a**: 90% yield; mp 105−107 °C; $[\alpha]_D$ −1.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3429, 1795, 1752, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (m, 12H), 1.54 (d, 3H, *J* = 6.6 Hz), 4.46 (d, H, *J* = 4.4 Hz), 4.58 (dq, H, *J* = 4.4, 6.6 Hz), 5.23 (s, 2H), 5.30 (br s, 1H), 5.43 (dq, 1H, *J* = 6.2, 7.8 Hz), 7.27−7.40 (m, H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.1, 21.1, 28.2, 49.2, 61.9, 67.9, 73.7, 79.6, 128.3, 128.7, 134.6, 151.1, 154.6, 167.4, 173.9. Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.43): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.07; H, 6.48; N, 6.88.

Boc-L-Ala-D-Oxd-OH (3b). For the synthetic procedure from **2b** see the above preparation of **3a**: quantitative yield; mp 56−58 °C; $[\alpha]_D$ −3.1 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3436, 1799, 1747, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32−1.45 (m, 12H), 1.56 (d, 3H, *J* = 6.2 Hz), 4.42 (d, 1H, *J* = 3.4 Hz), 4.62−4.80 (m, 1H), 5.35−5.49 (m, 1H), 6.38 (d, 1H, *J* = 6.2 Hz), 9.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.7, 21.2, 28.2, 49.1, 61.8, 74.1, 80.7, 151.6, 155.5, 170.1, 173.7. Anal. Calcd for $C_{14}H_{24}N_2O_7$ (332.35): C, 50.59; H, 7.28; N, 8.43. Found: C, 50.62; H, 7.52; N, 8.40.

H-L-Ala-D-Oxd-OBn·CF_3CO_2H (4b). For the synthetic procedure from **2b** see the above preparation of **4a**: quantitative yield; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (d, H, *J* = 6.3 Hz), 1.65 (d, 3H, *J* = 6.9 Hz), 4.55 (d, 1H, *J* = 3.9 Hz), 4.62 (dq, 1H, *J* = 3.9, 6.3 Hz), 5.13−5.32 (m, 4H), 7.32−7.45 (m, 5H), 7.82 (br s, 3H).

Boc-(L-Ala-D-Oxd)$_2$-OBn (5b). For the synthetic procedure from **3b** and **4b** see the above preparation of **5a**: 85% yield; mp 199−203 °C; $[\alpha]_D$ +3.6 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3445, 1790, 1720, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.40 (d, 3H, *J* = 6.0 Hz), 1.42 (s, 9H), 1.49 (d, 3H, *J* = 7.0 Hz), 1.52 (d, 3H, *J* = 6.0 Hz), 1.53 (d, 3H, *J* = 6.2 Hz), 4.42 (d, 1H, *J* = 4.8 Hz), 4.45 (d, 1H, *J* = 4.2 Hz), 4.57 (dq, 1H, *J* = 4.2, 6.3 Hz), 4.72 (dq, 1H, *J* = 6.0 Hz), 5.10 (br s, 1H), 5.23 (AB, 2H, *J* = 12.2 Hz), 5.28 (dq, 1H, *J* = 6.0, 6.9 Hz), 5.57 (dq, 1H, *J* = 7.0 Hz), 7.14 (d, 1H, *J* = 7.0 Hz), 7.30−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.0, 20.9, 21.0, 28.2, 48.7, 49.3, 62.0, 62.9, 67.9, 73.8, 75.0, 80.2, 128.2, 128.6, 134.7, 151.2, 151.7, 155.4, 166.8, 167.3, 172.3, 174.3. Anal. Calcd for $C_{28}H_{36}N_4O_{11}$ (604.24): C, 55.62; H, 6.00; N, 9.27. Found: C, 55.67; H, 6.04; N, 9.23.

Boc-(L-Ala-D-Oxd)$_2$-OH (6b). For the synthetic procedure from **5b** see the above preparation of **3a**: quantitative yield; mp 138 °C dec; $[\alpha]_D$ −16.0 (*c* 1.0, MeOH); IR (Nujol) ν = 3548, 3361, 1788, 1674 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 1.35 (d, 3H, *J* = 6.8 Hz), 1.42−1.46 (m, 12H), 1.52 (d, 3H, *J* = 5.8 Hz), 1.55 (d, 3H, *J* = 6.0 Hz), 4.48−4.78 (m, 4H), 5.30 (q, 1H, *J* = 7.4 Hz), 5.55 (q, 1H, *J* = 6.8 Hz); ^{13}C NMR (CD_3OD, 50 MHz) δ 17.7, 18.0, 20.8, 21.2, 28.7, 49.9, 50.3, 63.1, 64.6, 76.1, 76.5, 80.7, 153.4, 153.7, 157.5, 169.7, 171.2, 173.6, 175.2. Anal. Calcd for $C_{21}H_{30}N_4O_{11}$ (514.19): C, 49.02; H, 5.88; N, 10.89. Found: C, 49.11; H, 5.83; N, 10.78.

Boc-(L-Ala-D-Oxd)$_3$-OBn (7b). For the synthetic procedure from **6b** and **4b** see the above preparation of **5a**: 82% yield; mp 128−131 °C; $[\alpha]_D$ −25.9 (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3440, 3401, 3390, 1793, 1721, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (d, 3H, *J* = 6.8 Hz), 1.40 (s, 9H), 1.42−1.55 (m, 15H), 4.45 (d, 1H, *J* = 4.4 Hz), 4.48 (d, 1H, *J* = 3.6 Hz), 4.61−4.74 (m, 4H), 5.17−5.46 (m, 5H), 5.48−5.58 (m, 1H), 7.28−7.39 (m, 5H), 7.47 (br s, 1H), 7.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 16.4, 17.1, 20.5, 20.6, 20.8, 28.2, 48.6, 48.8, 49.4, 61.6, 62.4, 62.6, 68.5, 74.2, 75.1, 75.3, 80.5, 128.4, 128.5, 128.7, 134.6, 151.6, 151.9, 155.8, 168.2, 168.4, 172.5, 173.0, 174.6. Anal. Calcd for $C_{36}H_{46}N_6O_{15}$ (802.30): C, 53.86; H, 5.78; N, 10.47. Found: C, 53.88; H, 5.76; N, 10.45.

Boc-(L-Ala-D-Oxd)$_3$-OH (8b). For the synthetic procedure from **7b** see the above preparation of **3a**: quantitative yield; mp 177 °C dec; $[\alpha]_D$ −9.3 (*c* 1.0, MeOH); IR (Nujol) ν = 3579, 3411, 3358, 1780, 1721, 1676 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz) δ 1.22 (d, 3H, *J* = 6.0 Hz), 1.26−1.32 (m, 15H), 1.38 (d, 3H, *J* = 7.2 Hz), 1.40 (d, 3H, *J* = 7.2 Hz), 1.42 (d, 3H, *J* = 6.0 Hz), 4.32−4.35 (m, 1H), 4.38−4.40 (m, 2H), 4.50−4.63 (m, 3H), 5.14−5.17 (m, 1H), 5.24−5.27 (m, 1H), 5.42−5.45 (m, 1H); ^{13}C NMR (CD_3OD 50 MHz) δ 17.0, 17.8, 18.2, 20.9, 21.0, 21.2, 28.8, 49.5, 50.2, 50.4, 63.3, 64.4, 64.5, 76.2, 76.7, 76.8, 80.9, 153.5, 153.7, 157.5, 169.8, 170.2, 171.5, 173.9, 174.0, 175.4, 187.7. Anal. Calcd for $C_{29}H_{40}N_6O_{15}$ (712.26): C, 48.87; H, 5.66; N, 11.79. Found: C, 48.90; H, 5.64; N, 11.74.

Boc-(L-Ala-D-Oxd)$_4$-OBn (9b). For the synthetic procedure from **8b** and **4b** see the above preparation of **5a**: 83% yield; mp 120 °C; $[\alpha]_D$ −51.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3441, 3350, 3287, 1788, 1742, 1708, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37−1.59 (m, 33H), 4.42−4.75 (m, 5H), 4.91−5.02 (m, 3H), 5.18−5.30 (m, 3H), 5.35−5.58 (m, 4H), 5.62−5.90 (m, 2H), 5.96−6.08 (m, 1H), 7.30−7.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 21.1, 21.2, 21.3, 28.5, 49.2 (four signals), 62.1, 62.8, 74.5, 75.2, 75.5, 82.3, 128.8,

129.1, 129.3, 135.1, 151.2, 152.2, 167.2, 168.3, 169.2, 173.3, 174.0. Anal. Calcd for $C_{44}H_{56}N_8O_{19}$ (1000.37): C, 52.80; H, 5.64; N, 11.19. Found: C, 52.77; H, 5.62; N, 11.22.

Boc-(L-Ala-D-Oxd)$_4$-OH (10b). For the synthetic procedure from **9b** see the above preparation of **3a**: quantitative yield; mp 174 °C dec; $[\alpha]_D$ −18.9 (*c* 0.8, MeOH); IR (Nujol) ν = 3403, 3269, 1789, 1669 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.34 (d, 3H, J = 6.8 Hz), 1.40 (d, 3H, J = 7.2 Hz), 1.41−1.45 (m, 15H), 1.49 (d, 3H, J = 6.4 Hz), 1.50 (d, 3H, J = 6.4 Hz), 1.51 (d, 3H, J = 7.6 Hz), 1.52 (d, 3H, J = 6.8 Hz), 4.61−4.78 (m, 8H), 5.30 (q, 1H, J = 6.8 Hz), 5.42 (q, 1H, J = 6.8 Hz), 5.48−5.56 (m, 1H), 5.60−5.72 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.4, 16.5, 17.2, 17.4, 19.6, 19.7, 19.8, 20.1, 27.6, 48.6, 48.8, 48.9, 49.1, 61.8, 62.6, 62.8, 63.1, 75.0, 75.2, 75.3, 75.4, 79.4, 152.2, 152.3, 152.4, 152.6, 163.7, 168.7, 168.8, 172.1, 172.3. Anal. Calcd for $C_{37}H_{50}N_8O_{19}$ (910.32): C, 48.79; H, 5.53; N, 12.30. Found: C, 48.70; H, 5.61; N, 12.25.

Boc-(L-Ala-D-Oxd)$_5$-OBn (11b). For the synthetic procedure from **10b** and **4b** see the above preparation of **5a**: 78% yield; mp 210 °C; $[\alpha]_D$ −73.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3354, 3296, 1790, 1741, 1707, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35−1.62 (m, 39H), 4.41−4.88 (m, 7H), 4.91−5.08 (m, 3H), 5.18−5.56 (m, 5H), 5.83 (dq, 1H, J = 6.2 Hz), 5.93 (dq, 1H, J = 6.0 Hz), 6.07 (dq, 1H, J = 6.0 Hz), 7.30−7.42 (m, 5H), 7.85−8.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 18.1, 18.3, 19.1, 19.5, 20.1, 20.6, 20.7, 20.9, 21.3, 28.4, 48.9 (four signals), 74.9, 78.7, 128.3, 128.9, 129.2, 134.3, 150.4, 150.9, 151.3, 151.8, 155.0, 167.4, 168.1, 168.5, 168.7, 170.0, 171.3, 171.5, 172.1, 172.4. Anal. Calcd for $C_{52}H_{66}N_{10}O_{23}$ (1198.43): C, 52.08; H, 5.55; N, 11.68. Found: C, 52.11; H, 5.57; N, 11.70.

Boc-(L-Ala-D-Oxd)$_5$-OH (12b). For the synthetic procedure from **11b** see the above preparation of **3a**: quantitative yield; mp 180 °C dec; $[\alpha]_D$ −56.4 (*c* 1.0, MeOH); IR (Nujol) ν = 3410, 1779, 1686, 1627 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.43−1.48 (m, 24H), 1.51−1.58 (m, 15H), 4.47−5.15 (m, 10H), 5.35−5.45 (m, 2H), 5.85−6.15 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 18.1, 18.9, 20.3, 21.2, 21.3, 21.4, 21.5, 21.6, 29.2, 50.4, 50.6, 50.7, 63.2, 63.8 (four signals), 76.5, 76.7, 80.6, 153.6, 154.1, 170.2, 170.4, 170.5, 170.6, 172.9, 173.0, 174.3. Anal. Calcd for $C_{45}H_{60}N_{10}O_{23}$ (1108.38): C, 48.74; H, 5.45; N, 12.63. Found: C, 48.81; H, 5.49; N, 12.59.

Boc-(L-Ala-D-Oxd)$_6$-OBn (13b). For the synthetic procedure from **12b** and **4b** see the above preparation of **5a**: 70% yield; mp 185 °C dec; $[\alpha]_D$ −101.0 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2, 3 mM) ν = 3352, 3295, 1787, 1739, 1706, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39−1.49 (m, 18H), 1.49−1.62 (m, 27H), 4.46−4.59 (m, 7H), 4.73−4.78 (m, 1H), 4.95−4.98 (m, 1H), 5.00−5.03 (m, 1H), 5.05−5.09 (m, 1H), 5.24 (br s, 3H), 5.24−5.28 (m, 1H), 5.60−5.67 (m, 2H), 5.75−5.98 (m, 2H), 5.98−6.08 (m, 1H), 7.32−7.41 (m, 5H), 7.94 (br s, 1H), 8.15 (br s, 1H), 8.31 (br s, 1H), 8.47 (br s, 1H), 8.53 (br s, 1H); ^{13}C NMR (CD_3CN, 100 MHz) δ 17.5, 17.8, 20.8, 21.0, 21.1, 28.5, 48.9, 49.4, 49.8, 62.1, 62.6, 63.3, 68.6, 75.2, 76.0, 76.2, 77.6, 129.2, 129.5, 129.6, 136.3, 153.0, 169.1, 169.6, 170.7, 173.6. Anal. Calcd for $C_{60}H_{76}N_{12}O_{27}$ (1396.50): C, 51.57; H, 5.48; N, 12.03. Found: C, 51.61; H, 5.46; N, 12.08.

Boc-(L-Ala-D-Oxd)$_6$-OH (14b). For the synthetic procedure from **13b** see the above preparation of **3a**: quantitative yield; mp 230 °C dec; $[\alpha]_D$ −118.7 (*c* 0.4, CH_2Cl_2); IR (Nujol) ν = 3280, 1789, 1709, 1660 cm^{-1}; ^{1}H NMR (CD_3CN, 600 MHz) δ 1.38−1.59 (m, 45H), 4.37−4.62 (m, 6H), 4.64−5.26 (m, 7H), 5.28−6.18 (m, 6H), 7.09 (br s, 1H), 8.05−8.58 (br s, 4H); ^{13}C NMR (CD_3OD, 100 MHz) δ 16.7, 17.6, 17.8, 19.9, 20.1, 20.3, 28.0, 49.0, 61.4, 62.1, 75.2, 76.8, 152.1, 168.9, 171.4, 172.5. Anal. Calcd for $C_{53}H_{70}N_{12}O_{27}$ (1306.45): C, 48.70; H, 5.40; N, 12.86. Found: C, 48.63; H, 5.41; N, 12.89.

Boc-Aib-L-Oxd-OBn (2c). To a stirred solution of Boc-Aib-OH (0.51 g, 2.5 mmol) in acetonitrile (20 mL) were added HBTU (0.98 g, 2.6 mmol), then **1a** (0.59 g, 2.5 mmol), and finally DBU (0.75 mL, 5 mol). The mixture was stirred for 30 min, and then acetonitrile was removed under reduced pressure and was replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. Product **2c** was obtained pure in 60% yield (0.63 g) as a waxy solid after silica gel chromatography (cyclohexane/ethyl acetate, 9:1, as eluant): mp 114−115 °C; $[\alpha]_D$ −54.4 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3448, 1793, 1754, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H, *t*-Bu), 1.47 (d, 3H, J = 6.0 Hz, CH_3-Oxd), 1.56 (s, 3H, CH_3-Aib), 1.60 (s, 3H, CH_3-Aib), 4.48−4.60 (m, 2H, CHN + CHO), 5.22 (AB, 2H, J = 12.1 Hz, OC*H*$_2$Ph), 5.44 (s, 1H, NH), 7.23−7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 23.9, 26.6, 28.5, 57.5, 63.4, 68.1, 73.6, 80.1, 128.6, 128.9, 134.9, 151.2, 155.1, 168.7, 174.9. Anal. Calcd for $C_{21}H_{28}N_2O_7$ (420.46): C, 59.99; H, 6.71; N, 6.66. Found: C, 59.97; H, 6.74; N, 6.65.

Boc-Aib-L-Oxd-OH (3c). For the synthetic procedure from **2c** see the above preparation of **3a**: quantitative yield; mp 204−205 °C; $[\alpha]_D$ −77.1 (*c* 1.0, acetone); IR (CH_2Cl_2, 3 mM) ν = 3445, 1792, 1745, 1706, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H, *t*-Bu), 1.51 (d, 3H, J = 6.2 Hz, CH_3-Oxd), 1.56 (s, 3H, CH_3-Aib), 1.62 (s, 3H, CH_3-Aib), 4.47 (d, 1H, J = 2.2 Hz, CHN-Oxd), 4.77 (dq, 1H, J = 2.2, 6.2 Hz, CHO), 6.30 (s, 1H, NH); ^{13}C NMR (acetone-d_6, 50 MHz) δ 19.6, 22.4, 25.3, 27.0, 56.4, 62.2, 72.8, 77.9, 150.0, 153.9, 168.8, 173.6. Anal. Calcd for $C_{14}H_{22}N_2O_7$ (330.33): C, 50.90; H, 6.71; N, 8.48. Found: C, 50.86; H, 6.73; N, 4.51.

H-Aib-L-Oxd-OBn (4c). A solution of **2a** (1 mmol, 0.42 g) and TFA (18 mmol, 1.39 mL) in dry methylene chloride (10 mL) was stirred for 4 h at room temperature, and then the volatiles were removed under reduced pressure and replaced with pure methylene chloride (20 mL). The mixture was washed with brine and with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The product was obtained pure in 95% yield (0.30 g) without any further purification: $[\alpha]_D$ +3.0 (*c* 0.8, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3444, 1789, 1754, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, 3H, J = 6.0 Hz, CH_3-Oxd), 1.47 (s, 6H), 4.62 (dq, 1H, J = 4.6, 6.0 Hz), 4.82 (d, 1H, J = 4.6 Hz), 5.23 (s, 2H), 7.23−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 24.8, 30.8, 59.2, 59.8, 66.3, 67.8, 72.8, 128.5, 128.8, 129.0, 134.2, 152.8, 167.1, 178.4. Anal. Calcd for $C_{16}H_{20}N_2O_5$ (320.34): C, 59.99; H, 6.29; N, 8.74. Found: C, 60.01; H, 6.31; N, 8.76.

Boc-(Aib-L-Oxd)$_2$-OBn (5c). To a stirred solution of **3c** (1 mmol, 0.33 g) and HATU (1 mmol, 0.38 g) in dry acetonitrile (10 mL) under an inert atmosphere was added a mixture of **4c** (1 mmol, 0.32 g) and Et_3N (2 mmol, 0.29 mL) in dry acetonitrile (10 mL) at room temperature. The solution was stirred for 40 min under an inert atmosphere, and then acetonitrile was removed under reduced pressure and was replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 8:2, as eluant) in 55% yield (0.35 g): mp 136−138 °C; $[\alpha]_D$ −63.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 mM) ν = 3446, 3375, 1789, 1726, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.27 (d, 3H, J = 6.2 Hz), 1.45 (s, 9H), 1.54 (d, 3H, J = 6.2 Hz), 1.63 (s, 3H), 1.67 (s, 6H), 1.72 (s, 3H), 3.99 (dq, 1H, J = 1.4, 6.2 Hz), 4.38−4.45 (m, 1H), 4.63 (d, 1H, J = 5.4 Hz), 4.92 (AB, 2H, J = 12.2 Hz), 5.48 (s, 1H), 5.51 (d, 1H, J = 1.4 Hz), 7.01−7.31 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 20.3, 21.4, 22.8, 23.7, 26.4, 28.3, 57.2, 60.0, 64.5, 64.8, 65.7, 73.8, 79.8, 128.4, 128.7, 128.8, 134.6, 151.3, 154.0, 154.8, 166.4, 167.1, 175.0, 175.6. Anal. Calcd for $C_{30}H_{40}N_4O_{11}$ (632.66): C, 56.95; H, 6.37; N, 8.86. Found: C, 56.92; H, 6.40; N, 8.83.

Boc-(Aib-L-Oxd)$_2$-OH (6c). For the synthetic procedure from **5c** see the above preparation of **3a**: quantitative yield; mp 204−206 °C; $[\alpha]_D$ −115.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 3 × 10^{-3} M) ν = 3443, 1792, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 3H), 1.43 (s, 9H), 1.55 (d, 3H, J = 6.2 Hz), 1.60 (s, 3H), 1.65 (s, 3H), 1.70 (s, 3H), 1.73 (s, 3H), 4.56 (dq, 1H, J = 1.4, 6.2 Hz), 4.60 (dq, 1H, J = 5.0, 6.2 Hz), 4.80 (d, 1H, J = 5.0 Hz), 5.41 (d, 1H, J = 1.4 Hz), 5.59 (s, 1H),

6.58 (br s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 20.5, 21.7, 23.0, 24.0, 26.5, 28.5, 57.4, 59.8, 64.7, 65.0, 65.8, 74.2, 76.5, 77.2, 77.8, 80.5, 151.4, 154.1, 155.0, 167.1, 168.5, 174.9, 175.7. Anal. Calcd for $C_{23}H_{34}N_4O_{11}$ (542.54): C, 50.92; H, 6.32; N, 10.33. Found: C, 50.88; H, 6.30; N, 10.38.

Boc-Aib-L-Oxd-Aib-D-Oxd-OBn (7c). To a stirred solution of **3c** (1 mmol, 0.33 g) and HATU (1 mmol, 0.38 g) in dry acetonitrile (10 mL) under an inert atmosphere was added a mixture of H-Aib-D-Oxd-OBn (1 mmol, 0.32 g) and Et_3N (2 mmol, 0.29 mL) in dry acetonitrile (10 mL) at room temperature. The solution was stirred for 40 min under an inert atmosphere, and then acetonitrile was removed under reduced pressure and was replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 8:2, as eluant) in 53% yield (0.34 g) as a waxy solid: $[\alpha]_D$ −63.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, 1 × 10^{-3} M) ν = 3437, 1787, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, 3H, *J* = 6.9 Hz), 1.43 (s, 9H), 1.53 (d, 3H, *J* = 6.3 Hz), 1.62 (s, 3H), 1.65 (s, 3H), 1.68 (s, 6H), 4.50 (dq, 1H, *J* = 1.5, 6.3 Hz), 4.60−4.65 (m, 1H), 4.77 (d, 1H, *J* = 4.5 Hz), 5.20 (d, 1H, *J* = 12.0 Hz), 5.26 (d, 1H, *J* = 12.0 Hz), 5.33 (d, 1H, *J* = 1.5 Hz), 5.52 (br s, 1H), 7.22−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 20.2, 21.5, 22.7, 23.7, 26.4, 28.3, 57.2, 60.3, 64.4, 65.9, 68.3, 73.8, 79.8, 128.5, 128.7, 128.8, 134.5, 151.3, 153.5, 154.9, 166.5, 167.2, 175.1, 176.1. Anal. Calcd for $C_{30}H_{40}N_4O_{11}$ (632.66): C, 56.95; H, 6.37; N, 8.86. Found: C, 56.98; H, 6.41; N, 8.83.

Boc-Aib-L-Oxd-Aib-D-Oxd-OH (8c). For the synthetic procedure from **7c** see the above preparation of **3a**: quantitative yield; mp 147 °C dec; $[\alpha]_D$ −67.0 (*c* 0.2, MeOH); IR (Nujol) ν = 33373, 3173, 1794, 1732, 1705 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.40−1.44 (m, 9H), 1.51 (s, 3H), 1.53 (d, 3H, *J* = 6.4 Hz), 1.60 (s, 3H), 1.64 (s, 3H), 1.68 (s, 3H), 4.46 (dq, 1H, *J* = 1.6, 7.2 Hz), 4.55 (d, 1H, *J* = 7.2 Hz), 4.72 (dq, 1H, *J* = 1.6, 6.0 Hz), 5.41 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 21.8, 22.2, 22.8, 23.7, 27.0, 27.8, 28.8, 54.6, 58.2, 60.2, 65.0, 65.2, 65.8, 75.1, 152.7, 154.7, 168.6, 169.7, 176.3, 176.4. Anal. Calcd for $C_{23}H_{34}N_4O_{11}$ (542.54): C, 50.92; H, 6.32; N, 10.33. Found: C, 50.98; H, 6.38; N, 10.27.

X-ray Structure Determination. The X-ray intensity data for **2c** were measured on a Bruker AXS SMART 2000 diffractometer, equipped with a CCD detector using Mo Kα radiation. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in 3 sets of 20 exposures, collected in 3 different ω regions, and eventually refined against all data. A full sphere of reciprocal space was scanned by 0.3° ω steps, with the detector kept at 5.0 cm from the sample. The software SMART[21] was used for collecting frames of data, indexing reflections, and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program,[22] and an empirical absorption correction was applied using SADABS.[23] The structure was solved by direct methods (SIR 97[24]) and subsequent Fourier synthesis, and refined by full-matrix least squares on F^2 (SHELXTL[25]), using anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms, except the amidic hydrogen which was located in the Fourier map and refined isotropically, were added in calculated positions, included in the final stage of refinement with isotropic thermal parameters, U(H) = 1.2U_{eq}(C) [U(H) = 1.5U_{eq}(C-Me)], and allowed to ride on their carrier carbons. Crystallographic parameters for **2c** are reported in the Supporting Information.

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Supporting Information Available: Crystallographic data and structure refinement parameters for **2c** and a dilution series of ^{1}H NMR spectra of **11b** in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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