Synthesis of Oligomers of *trans*-(4*S*,5*R*)-4-Carboxybenzyl 5-Methyl Oxazolidin-2-one: An Approach to New Foldamers

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The synthesis of two oligomers containing three and four residues, respectively, of *trans*-(4*S*,5*R*)-4-carboxy 5-methyloxazolidin-2-ones is described. The monomer is obtained by starting from benzyl-*N*-Boc-(3*R*)-aminobutanoate, by cyclization into the corresponding *trans*-(2*S*,3*R*)-2-carboxybenzyl-3-methyl-*N*-Boc-aziridine and rearrangement of the product to *trans*-(4*S*,5*R*)-4-carboxybenzyl-5-methyloxazolidin-2-one, catalyzed by $Sn(OTf)_2$. The oligomers are synthesized by activating the carboxy group as its pentaflourophenyl ester. The trimer and the tetramer are obtained in good yield, and their ^1H NMR spectra suggest that these molecules fold in ordered structures, where the C-4 hydrogen of a ring is always close to the carbonyl of the next ring. This result shows that the 4-carboxy-5-substituted-oxazolidin-2-ones are a new class of pseudoprolines which fully control the formation of a $Xaa_{i-1}-Pro_i$ peptide bond in the *trans* conformation and are complementary to the pseudoprolines obtained from cyclocondensation of cysteine, serine, or threonine and aldehydes or ketones, which strongly favor the $Xaa_{i-1}-Pro_i$ peptide bond in the *cis* conformation.

Introduction

Gellman has suggested the term "foldamers" for novel oligomers which have a tendency to adopt a specific compact conformation.[1] The main characteristics of a new foldamer should be (i) the identification of new polymeric backbones with suitable folding propensities; (ii) the introduction of interesting chemical functions in the foldamer; (iii) the discovery of an efficient synthetic pathway, which generally includes preparation of the monomers in enantiomerically pure form and optimization of the polymer synthesis.

The first step in foldamer design must therefore be to identify new backbones with well-defined secondary structural preferences;[2] for instance, conformationally constrained amino acids provide access to short sequences of peptide mimetics with secondary structure.[3] So as good monomers for the oligomerization reaction we envisaged the *trans*-4-carboxymethyl-5-alkyl/aryl-oxazolidin-2-ones, whose synthesis has been recently described, starting from racemic β-amino acids.[4] The key step for the preparation of these heterocycles is the rearrangement of 2-carboxymethyl-3-alkyl/aryl-*tert*-butyloxycarbonyl-aziridines to oxazolidin-2-ones, catalyzed by a Lewis acid (Figure 1).[5] The reaction proceeds with total regio- and stereoselectivity and can afford a wide range of 5-carboxyoxazolidin-2-ones, simply by changing the starting β-amino acid.

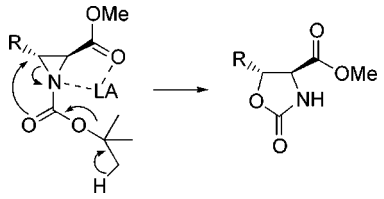

Figure 1. Mechanism for the rearrangement of *trans*-2-carboxymethyl-3-alkyl/aryl-*tert*-butyloxycarbonyl-aziridines to *trans*-4-carboxymethyl-5-alkyl/aryl-oxazolidin-2-ones.

These heterocycles can be considered as new pseudoprolines (ΨPro).[6] This term has recently been introduced to indicate synthetic proline analogues which are usually obtained by cyclocondensation of the amino acids cysteine, threonine, or serine with aldehydes or ketones. The conformation concerning the ΨPro-preceding peptide has been studied, because the propensity of the amino acid proline for forming a $Xaa_{i-1}-Pro_i$ *cis* peptide bond can be strongly enhanced by the introduction of a pseudoproline residue.

Results and Discussion

We report here the synthesis of enantiomerically pure *trans*-(4*S*,5*R*)-4-carboxybenzyl-5-methyl-*N*-Boc-oxazolidin-2-one **6** (Scheme 1), whose oligomerization affords a molecule which can be envisaged as a new foldamer with

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(6) (a) Wittelsberger, A.; Keller, M.; Scarpellino, L.; Patiny, L.; Acha-Orbea, H.; Mutter, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1111. (b) Mutter, M.; Haack, T. *Tetrahedron Lett.* **1992**, *33*, 1589. (c) Tam, J. P.; Miao, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9013.

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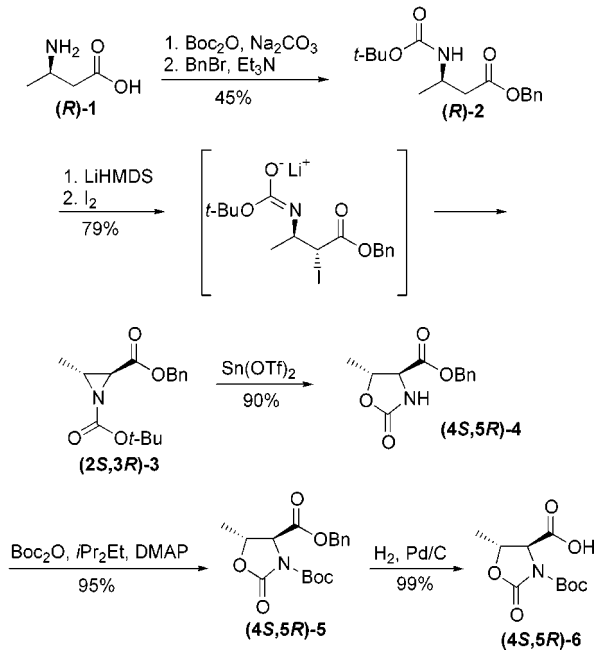
Scheme 1. Synthesis of Benzyl Ester 4 and *N*-Boc Derivative 6 of the Monomer



interesting properties. In particular, we will study the role of the carbonyl of the heterocyclic ring, which in principle should impart an ordered structure to the oligomer.

The preparation of the monomer was carried out starting from the enantiomerically pure (3*R*)-aminobutanoic acid **1**, obtained by enzymatic hydrolysis of the corresponding racemic *N*-phenylacetyl amide with penicyllin G acylase (PGA).[7] Preferentially this enzyme hydrolyzes the L (i.e., *S*) enantiomer, while the *R* is successively hydrolyzed with 6 M HCl at reflux. The (3*R*)-aminobutanoic acid is then transformed into **2** by protection of the amino group with Boc anhydride and sodium carbonate and of the carboxy group with benzyl bromide and triethylamine (Scheme 1). The benzyl was chosen as the protecting group of the carboxy function because it is removable by hydrogenolysis, which does not damage the heterocyclic ring. An HPLC analysis of **2** has shown that it was enantiomerically pure, and the result has been confirmed by comparing of the $[\alpha]_D$ with the data reported in the literature.[8]

The aziridine **3** was obtained by formation of the dianion of **2** with LiHMDS in dry THF and cyclization with iodine.[9] The reaction proceeded with the intermediate formation of the *anti* 2-iodo derivative which was immediately transformed into the heterocycle **3**. The *trans* aziridine was formed with high yield and diastereoselectivity (90:10 diastereomeric ratio from HPLC and ^{1}H NMR analysis) and was obtained pure after flash chromatography. The rearrangement to oxazolidin-2-one was performed by reaction with a catalytic amount of $Sn(OTf)_2$ which resulted to be the chosen reagent. The required oxazolidin-2-one **4** was obtained in quantitative yield and with complete regio- and stereoselectivity and can be used without any further purification.

To couple two molecules of (4*S*,5*R*)-4-carboxy-5-methyloxazolidin-2-one, we had to introduce a protecting group to the nitrogen and to activate the carboxy group. Many attempts were made in order to introduce a protecting group in quantitative yield, without damaging the heterocycle. Owing to the low reactivity of the nitrogen (which is a carbamate and not an amine), we tried to form the corresponding anion by reaction with LiHMDS at 0 °C and then to add some protecting reagents, such as Boc_2O, allyl bromide, and FMOC chloride (Cbz chloride was avoided, because it is not orthogonal with the benzyl ester). The results were poor in all cases, and the protected compound was obtained in 20−30% yield only by reaction with Boc_2O. By replacing LiHMDS with iPr$_2$EtN (Hünig's base) and a catalytic amount of DMAP and performing the reaction in DMF, the desired *N*-Boc derivative **5** was obtained in quantitative yield. After catalytic hydrogenation in ethyl acetate, the *N*-protected acid **6** was obtained in 67% overall yield from **2**.

The introduction of an activating group on the carboxy function required some study. Ciufolini and co-workers[10] described the synthesis and the coupling of (4*S*,5*R*)-4-chlorocarbonyl-5-methyl-*N*-acetyloxazolidin-2-one, derived from threonine, by reaction of the carboxyl group with oxalyl chloride and DMF. According to the authors, the acid chloride is a reactive material and not easy to purify. In our hands, with the Boc as protecting group, the reaction afforded the desired acyl chloride in very poor yield, owing to the acid-sensitive Boc group. Indeed, in these conditions, deprotection occurs, and an unprotected acyl chloride is obtained. As Ciufolini found, this material is unstable and readily decomposes. So a pentaflourophenyl ester was synthesized, by reaction of the acid with pentafluorophenyl trifloroacetate and pyridine in DMF.[11] The activated ester was obtained in quantitative yield after working up with water but could not be chromatographed (Scheme 2).

The coupling with the COOH-protected monomer **4** was performed in dry DMF with iPr$_2$EtN (2.2 equiv) and DMAP at room temperature for 2 h. The yield is around 70%, but it is very sensitive to reaction conditions and can drop to about 30%, if the reaction is not carefully carried out. In any case we never isolated any byproduct, due to the hydrolysis of an heterocyclic ring. Dimer **8** was then obtained pure after flash chromatography.

The ^{1}H NMR spectrum of the dimer **8** showed an interesting outcome. The chemical shift of the C-4 hydrogen of an heterocycle resonates at 5.49 ppm, while the other resonates at 4.59 ppm, which is roughly the

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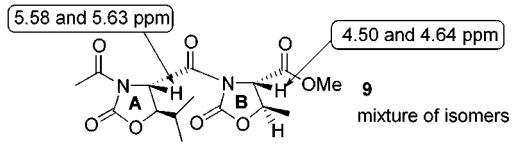
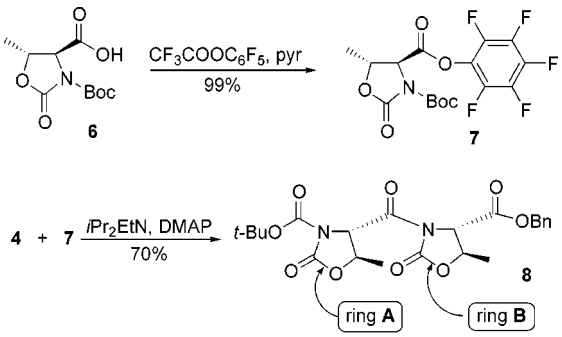


Figure 2. The structure and the more representative chemical shift of dimer **9** is reported. The molecule comes from the coupling of two racemates, so that a mixture of two diastereomers is obtained.

Scheme 2. Synthesis of the Dimer 9



same chemical shift recorded for the monomers **4** (4.01 ppm), **5** (4.34 ppm), and **6** (4.42 ppm). To understand the reason for this strong variation in chemical shift, we had to understand whether the shifted doublet belonged to ring **A** or to ring **B**. So we synthesized the racemic dimer **9**, containing a methyl and an isopropyl residue (Figure 2). A mixture of two diastereomers was obtained, so two doublets at 5.58 and 5.63 ppm and two doublets at 4.50 and 4.64 ppm were recorded. From ^{1}H NMR decoupling experiments, we could attribute the shifted doublets to C-4 hydrogen of ring **A**.

This anomalous chemical shift may be attributed to a rigid conformation assumed by the two oxazolidin-2-ones, which are nearly orthogonal one to the other. In this conformation, C-4 hydrogen of ring **A** results to be very near to the carbonyl at C-2 of ring **B**, which causes its strong deshielding. AM1 calculations performed on **8** confirm this prediction.[12] Indeed, by rotating the two bonds between ring **A** and ring **B**, four conformations of **8** corresponding to a minimum were found. Among them, the most stable conformation[13] is in agreement with our hypothesis (Figure 3). This result shows that the 4-carboxy-5-substituted-oxazolidin-2-ones are a new class of pseudoprolines which fully control the formation of a Xaa_{i-1}−Pro_i peptide bond in the *trans* conformation and are complementary to the pseudoprolines obtained from cyclocondensation of cysteine, serine, or threonine and aldehydes or ketones, which strongly favor the Xaa_{i-1}−Pro_i peptide bond in the *cis* conformation.[6a]

Bearing this result in mind, we felt that an oligomer of n elements should have $n - 1$ shifted doublets to be a foldamer. So we projected the synthesis of the corresponding tri- and tetra-4-carboxyoxazolidin-2-one, to verify if these oligomers had, respectively, two and three shifted doublets (Scheme 3). Some dimer **8** was hydrolyzed with trifluoroacetic acid in order to remove the Boc group. The reaction afforded the free NH **10** in quantitative yield, and no products obtained from the opening of the heterocycles were isolated. On the other hand, by reduction of the benzyl ester with hydrogen and palladium, the free acid **11** was obtained in quantitative yield. Both compounds can be utilized without any further purification. The acid was transformed in quantitative yield into the activated ester **12**, which was stable to workup, but could not be chromatographed. The synthesis of the trimer **13** and of the tetramer **14** was performed following the procedure that we had envisaged for the synthesis of the dimer **8**, in DMF in the presence of iPr$_2$EtN and DMAP. The trioxazolidin-2-one **13** and the tetraoxazolidin-2-one **14** were obtained in 55% and 50% yield, respectively, after flash chromatography.

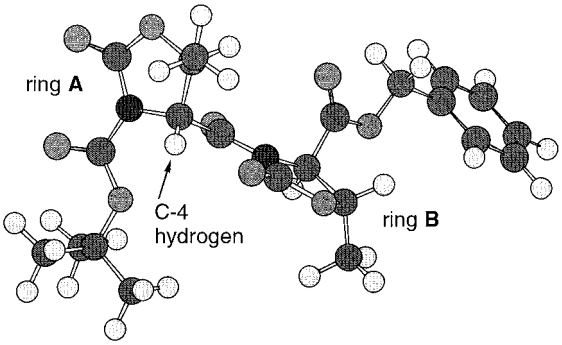
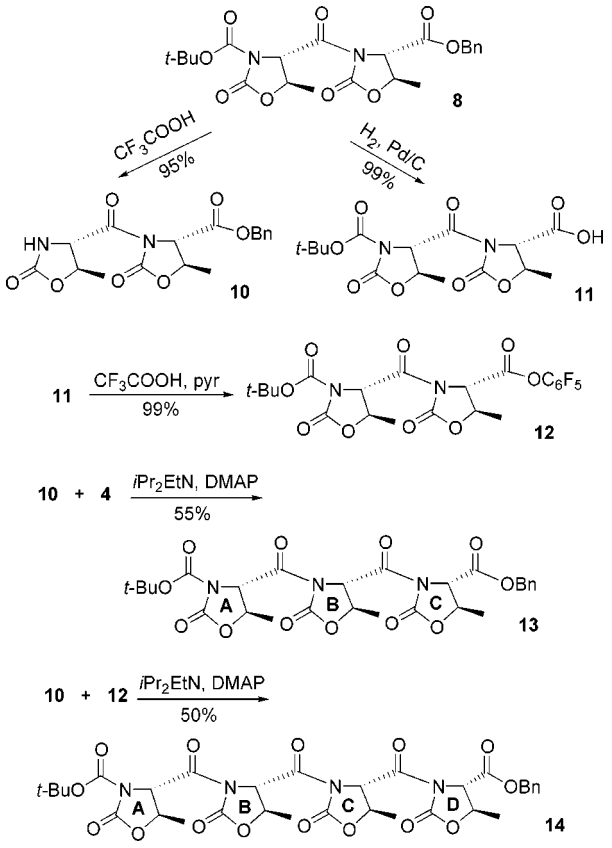


Figure 3. This conformation of **8** is in agreement with the lower minimum obtained with AM1 calculations and accounts for the anomalous chemical shift of C-4 hydrogen of ring **A**.

Scheme 3. Synthesis of the Trioxazolidin-2-one 13 and of the Tetraoxazolidin-2-one 14



The ^{1}H NMR spectra of **13** and **14** showed the expected results (Figure 4): in the trimer **13**, two of the three doublets of C-4 hydrogens of rings **A**, **B**, **C** are strongly

(12) The minimization was performed with semiempirical AM1 Hamiltonian using the integrated package MOPAC 2000.

(13) The most stable conformation of dimer **8** is reported in Figure 3 and is about 4 kcal/mol more stable than the closest alternative.

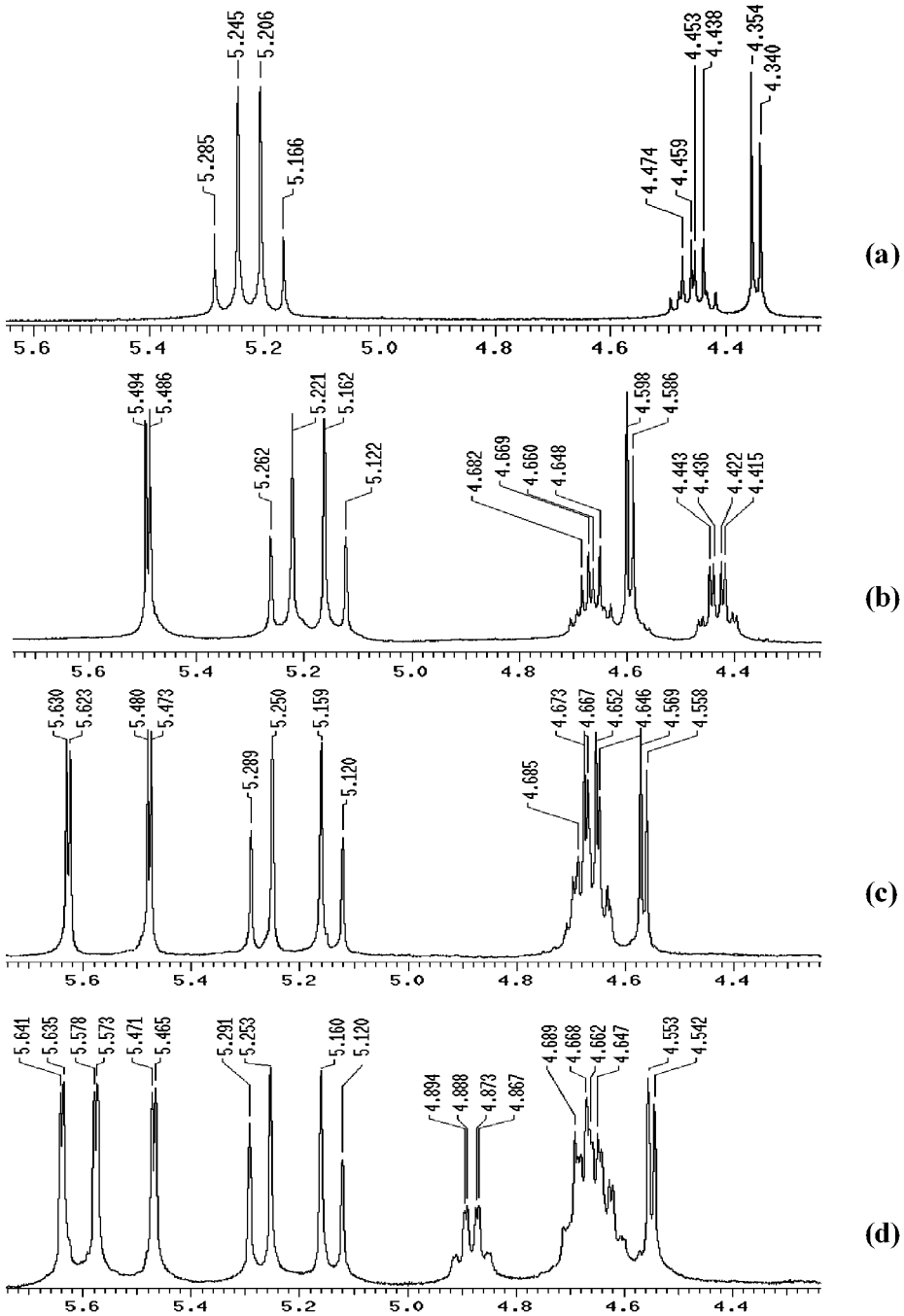


Figure 4. ^{1}H NMR of fully protected monomer **6** (a), dimer **8** (b), trimer **13** (c), and tetramer **14** (d). The areas regarding the ring hydrogen are reported.

deshielded and all resonate between 5.4 and 5.7 ppm, while the third resonates at 4.56 ppm. Following the same behavior, three of the four doublets of C-4 hydrogens of the tetramer **14** resonate between 5.4 and 5.7 ppm, while the fourth resonates at 4.55 ppm. From this outcome we can deduce that both the oligomers fold in ordered structures, where the C-4 hydrogens of the first rings are deshielded by the carbonyls of next rings, while the C-4 hydrogen of C-terminal rings is not deshielded, because it has no carbonyl groups nearby. Further studies are in progress on this subject.

Conclusions

In this paper we have shown a straightforward synthetic method for the preparation of enantiomerically pure (4*S*,5*R*)-4-carboxybenzyl-5-methyloxazolidin-2-ones. The method is quite general and can be utilized to obtain a wide range of 4-carboxybenzyl-5-alkyl/aryl-oxazolidin-2-ones. These compounds belong to the family of pseudoprolines, and their oligomerization was studied. So we have shown an approach for the preparation of a trimer and a tetramer of this heterocycle in good yield, avoiding the ring hydrolysis at all stages. ^{1}H NMR analysis of the trimer **13** and of tetramer **14** shows that two and three doublets respectively of the C-4 hydrogens are strongly deshielded, while the doublet of the C-4 hydrogen of the C-terminal ring is not: this effect can be attributed to the deshielding effect of carbonyls of the adiacent ring, which is always close to the hydrogen, thus showing that these oligomers fold in ordered structures.

Experimental Section

General. NMR spectra were recorded with spectrometers at 300 or 200 MHz (^{1}H NMR) and at 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. HPLC analysis was performed on a liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190−600 nm). HPLC grade 2-propanol and hexane were used as the eluting solvents. THF was distilled from sodium benzophenone ketyl.

Benzyl *N*-Boc-(3*R*)-Aminobutanoate 2. (3*R*)-Aminobutanoic acid hydrochloride (5 mmol, 0.52 g) was dissolved in a mixture of water (10 mL) and *tert*-butyl alcohol (15 mL), sodium carbonate (15 mmol, 1.59 g) and Boc anhydride (7.5 mmol, 1.64 g) were added in one portion, and the mixture was refluxed for 2 h. The mixture was cooled and acidified with 11 N HCl till pH = 1, and then *tert*-butyl alcohol was removed under vacuo and replaced with ethyl acetate. The organic layer was separated, washed twice with water, and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in acetone (10 mL), triethylamine (10 mmol, 1.4 mL) followed by benzyl bromide (5.5 mmol, 0.70 mL) was added in one portion at room temperature, and the mixture was stirred for 16 h. Water was added, acetone was removed under vacuo and replaced with ethyl acetate, the mixture was separated, and the organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant) and was obtained pure in 45% overall yield (0.69 g). Mp = 55−57 °C (lit.[8] 58−59 °C). IR (film): ν = 3367, 1728, 1678 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, 3H, J = 6.7 Hz), 1.44 (s, 9H, *t*-Bu), 2.48−2.64 (m, 2H), 3.92−4.18 (m, 1H), 4.90 (bs, 1H, NH), 5.12 (s, 2H), 7.22−7.51 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 20.5, 28.4, 40.8, 43.5, 66.3, 128.1, 128.3, 128.5, 135.6, 154.9, 171.2. $[\alpha]_D$ +17.3 (*c* 1, CH_2Cl_2) (lit.[8] $[\alpha]_D$ +17.5 (*c* 1, CH_2Cl_2). $C_{17}H_{25}NO_4$ (307.4): calcd C 66.43, H 8.20, N 4.56; found C 66.38, H 8.22, N 4.58.

(2*S*,3*R*)-*N*-Boc-2-Carboxybenzyl-3-methylaziridine 3. LiHMDS (5 mmol, 1 M soln in THF, 5 mL) was added to a stirred solution of benzyl *N*-Boc-(3*R*)-aminobutanoate **2** (2.5 mmol, 0.77 g) in dry THF (10 mL) under nitrogen atmosphere at −20 °C. The mixture was stirred 1 h and then was cooled to −60 °C, and iodine was added (3 mmol, 0.76 g) in dry THF (10 mL). The mixture was stirred 1 h, an aqueous saturated solution of ammonium thiosulfate was added, and THF was removed under reduced pressure and replaced with ethyl acetate. The organic layer was separated, washed twice with water, and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was obtained pure in 79% yield (0.60 g) as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant). IR (film): ν = 1745, 1726 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.31 (d, 3H, J = 5.1 Hz), 1.41 (s, 9H), 2.78−2.89 (m, 2H), 5.17 (2H, AB J = 12 Hz), 7.28−7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ = 20.9, 27.8, 39.6, 41.3, 67.1, 81.6, 128.2, 128.3, 128.4, 135.0, 158.7, 168.0. $[\alpha]_D$ +9.3 (*c* 0.5, CH_2Cl_2). $C_{17}H_{23}NO_4$ (305.4): calcd C 66.86, H 7.59, N 4.59; found C 66.90, H 7.62, N 4.57.

(4*S*,5*R*)-4-Carboxybenzyl-5-methyloxazolidin-2-one 4. To a stirred solution of *N*-Boc-aziridine **3** (1 mmol, 0.31 g) in dry methylene chloride (10 mL) was added $Zn(OTf)_2$ (0.1 mmol, 42 mg). The mixture was stirred 4 h under nitrogen at room temperature, additional methylene chloride and 5% aqueous solution of $NaHCO_3$ were added, the organic layer was separated, and the aqueous layer was acidified with 0.1 N aqueous HCl and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was obtained pure in 90% yield (0.21 g) as an oil after silica gel chromatography (cyclohexane/ethyl acetate 7:3 as eluant). IR (CH_2Cl_2): ν = 3453, 1777, 1748 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.51 (d, 3H, J = 6.3 Hz), 4.02 (d, 1H, J = 5.1 Hz), 4.69 (dq, 1H, J = 5.1, 6.3 Hz), 5.20 (AB, 2H, J = 12.3 Hz), 6.73 (bs, 1H, NH), 7.24−7.33 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ = 21.1, 27.6, 62.7, 67.8, 72.2, 84.5, 128.5, 128.6, 128.7, 134.5, 148.5, 167.3, 168.2. $[\alpha]_D$ +10.8 (*c* 0.5, CH_2Cl_2) (lit.[10] $[\alpha]_D$ +7.7 (*c* 0.49, CH_2Cl_2). $C_{12}H_{13}NO_4$ (235.2): calcd C 61.27, H 5.57, N 5.95; found C 61.32, H 5.53, N 4.99.

(4*S*,5*R*)-*N*-Boc-4-Carboxybenzyl-5-methyloxazolidin-2-one 5. To a stirred solution of oxazolidin-2-one **4** (1 mmol, 0.24 g) and Boc_2O (1.25 mmol, 0.27 g) in dry DMF (1 mL) were added *i*Pr_2EtN (1.1 mmol, 0.19 mL) and DMAP (0.1 mmol, 12 mg). The mixture was stirred 2 h under nitrogen at room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The fully protected oxazolidin-2-one **5** was obtained pure in 95% yield (0.32 g) as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant). IR (Nujol): ν = 1830, 1752, 1728 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H), 1.52 (d, 3H, J = 6.6 Hz), 4.34 (d, 1H, J = 4.5 Hz), 4.45 (dq, 1H, J = 4.5, 6.6 Hz), 5.22 (AB, 2H, J = 12.3 Hz), 7.24−7.45 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ = 21.1, 27.6, 62.7, 67.8, 72.2, 84.5, 128.5, 128.6, 128.7, 134.5, 148.5, 167.3. $[\alpha]_D$ −14.8 (*c* 1.2, CH_2Cl_2). $C_{17}H_{21}NO_6$ (335.4): calcd C 60.89, H 6.31, N 4.18; found C 66.90, H 6.33, N 4.22.

(4*S*,5*R*)-*N*-Boc-4-Carboxy-5-methyloxazolidin-2-one 6. To a solution of benzyl ester **5** (1 mmol, 0.34 g) in ethyl acetate (10 mL) was added 10% palladium on charcoal (30 mg), and the mixture was stirred in a Parr equipment with hydrogen (3 atm) for 1 h. Then the catalyst was filtered on a Celite pad, and the mixture was concentrated. The acid **6** was obtained in quantitative yield (0.24 g) without any further purification. Mp = 114−116 °C. IR (Nujol): ν = 3185, 1799, 1746, cm^{-1}. ^{1}H NMR (CD_3OD): δ = 1.50 (s, 9H), 1.52 (d, 3H, J = 6.2 Hz), 4.43 (d, 1H, J = 4.4 Hz), 4.58 (dq, 1H, J = 4.4, 6.2 Hz). ^{13}C NMR (CD_3OD): δ = 21.2, 28.0, 63.9, 74.5, 85.4, 150.2, 153.2, 171.7. $[\alpha]_D$ −16.2 (*c* 0.8, methanol). $C_{10}H_{15}NO_6$ (245.2): calcd C 48.98, H 6.17, N 5.71; found C 49.02, H 6.21, N 5.74.

Fully Protected Dioxazolidin-2-one 8. To a stirred solution of acid **6** (0.5 mmol, 123 mg) in dry DMF (1 mL) was added pyridine (0.55 mmol, 50 μL) followed by pentafluorophenyl triflouroacetate (0.63 mmol, 130 μL). The reaction was allowed to stir for 45 min at room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The pentaflourophenyl ester **7** was obtained in quantitative yield (206 mg), but could not be purified by silica gel chromatography. ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 9H), 1.62 (d, 3H, J = 6.3 Hz), 4.65−4.71 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 21.2, 27.6, 62.3, 72.1, 85.7, 136.2, 139.2, 139.6, 142.6, 148.1, 150.1, 164.8.

To a stirred solution of benzyl ester **5** (0.45 mmol, 106 mg), *i*Pr_2EtN (0.9 mmol, 263 μL), and DMAP (0.05 mmol, 6 mg) in dry DMF (1 mL) was added the pentaflourophenyl ester **7** (0.5 mmol, 206 mg) in dry DMF (1 mL) in one portion. The reaction was allowed to stir for 2 h at room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The dioxazolidin-2-one **8** was obtained pure in 70% yield (146 mg) as a waxy solid after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant). IR (Nujol): ν = 1826, 1795, 1750, 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9H), 1.55 (d, 3H, J = 6.2 Hz), 1.59 (d, 3H, J = 6.6 Hz), 4.45 (dq, 1H J = 2.2, 6.2 Hz), 4.61 (d, 1H, J = 3.5 Hz), 4.68 (dq, 1H, J = 3.5, 6.6 Hz), 5.21 (AB, 2H, J = 11.8 Hz), 5.51 (d, 1H, J = 2.2 Hz), 7.22−7.49 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 20.6, 21.2, 27.8, 61.1, 61.7, 68.6, 72.5, 74.7, 84.5, 128.5, 128.7, 128.9, 133.9, 149.2, 150.3, 151.8, 167.0, 168.0. $[\alpha]_D$ −64.2 (*c* 0.7, CH_2Cl_2). $C_{22}H_{26}N_2O_9$ (462.5): calcd C 57.14, H 5.67, N 6.06; found C 57.19, H 5.62, N 6.04.

Dioxazolidin-2-one NH 10. To a stirred solution of fully protected dioxazolidin-2-one **8** (0.2 mmol, 92 mg) in dry dichloromethane (10 mL) was added triflouroacetic acid (1.8 mmol, 0.45 mL). The reaction was allowed to stir for 3 h at room temperature, washed with 5% aqueous $NaHCO_3$ (2 × 10 mL), dried over sodium sulfate, and concentrated in vacuo. The *N*-deprotected dioxazolidin-2-one **10** was obtained pure in 95% yield (69 mg) as a waxy solid after silica gel chromatography

(cyclohexane/ethyl acetate 7:3 as eluant). IR (CH_2Cl_2): ν = 3431, 1784, 1772, 1714 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.56 (d, 3H, J = 6.4 Hz), 1.60 (d, 3H, J = 6.4 Hz), 4.59 (d, 1H, J = 4.2 Hz), 4.67 (dq, 1H, J = 4.2, 6.4 Hz), 4.83 (dq, 1H, J = 2.2, 6.4 Hz), 4.90 (d, 1H, J = 2.2 Hz), 5.23 (AB, 2H, J = 12.2 Hz), 5.81 (s, 1H, NH), 7.24−7.55 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ = 20.5, 21.2, 60.2, 61.5, 68.5, 74.8, 75.6, 128.5, 128.8, 128.9, 134.1, 144.4, 162.1, 167.1, 169.9. $[\alpha]_D$ −23.0 (*c* 0.4, CH_2Cl_2). $C_{17}H_{18}N_2O_7$ (362.3): calcd C 56.35, H 5.01, N 7.73; found C 56.42, H 5.08, N 7.69.

Dioxazolidin-2-one COOH 11. To a solution of fully protected dioxazolidin-2-one **8** (0.2 mmol, 92 mg) in ethyl acetate (10 mL) was added 10% palladium on charcoal (10 mg), and the mixture was stirred in a Parr equipment with hydrogen (3 atm) for 1 h. Then the catalyst was filtered on a Celite pad, and the mixture was concentrated. The acid **11** was obtained pure in quantitative yield (74 mg) without any further purification. IR (CH_2Cl_2): ν = 3437, 1827, 1807, 1722 cm^{-1}. ^1H NMR (CD_3OD): δ = 1.48 (s, 9H), 1.53 (d, 6H, J = 6.6 Hz), 1.57 (d, 3H, J = 6.3 Hz), 4.58 (d, 1H J = 3.3 Hz), 4.74 (dq, 1H, J = 2.5, 6.3 Hz), 4.82 (dq, 1H, J = 3.3, 6.3 Hz), 5.59 (d, 1H, J = 2.5 Hz), ^{13}C NMR ($CDCl_3$): δ = 20.7, 21.3, 27.9, 61.1, 62.0, 73.0, 75.0, 84.9, 152.1, 168.1. $[\alpha]_D$ −101.8 (*c* 0.2, CH_2Cl_2). $C_{15}H_{20}N_2O_9$ (372.3): calcd C 48.39, H 5.41, N 7.52; found C 48.38, H 5.44, N 7.55.

Fully Protected Trioxazolidin-2-one 13: To a stirred solution of acid **11** (0.1 mmol, 37 mg) in dry DMF (1 mL) was added pyridine (0.11 mmol, 11 μL) followed by pentafluorophenyl triflouroacetate (0.13 mmol, 32 μL). The reaction was allowed to stir for 45 min at room temperature, diluted with ethyl acetate (30 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The pentaflourophenyl ester **12** was obtained in quantitative yield (54 mg), but could not be purified by silica gel chromatography. ^1H NMR ($CDCl_3$): δ = 1.51 (s, 9H), 1.59 (d, 3H, J = 6.3 Hz), 1.71 (d, 3H, J = 6.0 Hz), 4.53 (dq, 1H, J = 2.2, 6.3 Hz), 4.80−4.95 (m, 2H), 5.51 (d, 1H, J = 2.2 Hz). ^{13}C NMR ($CDCl_3$): δ = 20.6, 21.2, 27.8, 60.8, 61.8, 72.8, 74.6, 85.2, 136.4, 139.7, 142.5, 150.8, 151.3, 163.9, 168.0.

To a stirred solution of (4*S*,5*R*)-4-carboxybenzyl-5-methyloxazolidin-2-one **4** (0.09 mmol, 21 mg), *i*Pr_2EtN (0.2 mmol, 57 μL), and DMAP (2 mg) in dry DMF (1 mL) was added pentaflourophenyl ester **12** (0.1 mmol, 54 mg) in dry DMF (1 mL) in one portion. The reaction was allowed to stir for 3 h at room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The trioxazolidin-2-one **13** was obtained pure in 55% yield (29 mg) as a white solid after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant). Mp = 83−85 °C (dec). IR (CH_2Cl_2): ν = 1832, 1786, 1747, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.51 (s, 9H), 1.59 (d, 3H, J = 6.6 Hz), 1.61 (d, 6H, J = 6.6 Hz), 4.56 (d, 1H, J = 3.6 Hz), 4.63−4.70 (m, 3H), 5.20 (AB, 2H, J = 12.0 Hz), 5.47 (d, 1H, J = 2.1 Hz), 5.63 (d, 1H, J = 1.8 Hz), 7.24−7.51 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 20.7, 21.3, 27.9, 61.0, 62.0, 68.8, 72.7, 75.2, 84.5, 128.6, 128.8, 129.1, 133.9, 148.6, 151.8, 152.2, 166.8, 168.4, 176.6. $[\alpha]_D$ −123.0 (*c* 0.6, CH_2Cl_2). $C_{27}H_{31}N_3O_{12}$ (589.6): calcd C 55.01, H 5.30, N 7.13; found C 55.08, H 5.33, N 7.08.

Fully Protected Tetraoxazolidin-2-one 14. To a stirred solution of dioxazolidin-2-one NH **10** (0.09 mmol, 33 mg), *i*Pr_2-EtN (0.2 mmol, 57 μL), and DMAP (2 mg) in dry DMF (1 mL) was added pentaflourophenyl ester **12** (0.1 mmol, 54 mg) in dry DMF (1 mL) in one portion. The reaction was allowed to stir for 3 h at room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 N aqueous HCl (2 × 30 mL), washed with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The tetraoxazolidin-2-one **14** was obtained pure in 50% yield as a white solid after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant). Mp = 94−97 °C (dec). IR (CH_2Cl_2): ν = 1827, 1786, 1751, 1722, 1607 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.52 (s, 9H), 1.59 (d, 6H, J = 6.6 Hz), 1.63 (d, 3H, J = 6.3 Hz), 1.67 (d, 3H, J = 6.3 Hz), 4.55 (d, 1H, J = 3.3 Hz), 4.58−4.73 (m, 3H), 4.87 (dq, 1H, J = 1.8, 6.3 Hz), 5.21 (AB, 2H, J = 11.8 Hz), 5.47 (d, 1H, J = 1.5 Hz), 5.57 (d, 1H, J = 1.5 Hz), 5.64 (d, 1H, J = 1.8 Hz), 7.22−7.49 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 20.7, 21.3, 28.0, 61.0, 61.1, 61.2, 62.0, 68.6, 72.6, 75.2, 75.4, 75.8, 84.5, 128.6, 128.8, 129.1, 133.9, 146.5, 156.5, 156.8, 166.7, 166.9, 167.2, 172.0, 177.7. $[\alpha]_D$ −142.0 (*c* 0.7, CH_2Cl_2). $C_{32}H_{36}N_4O_{15}$ (716.7): calcd C 53.63, H 5.06, N 7.82; found C 53.59, H 5.00, N 7.84.

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Supporting Information Available: ^1H NMR spectra of monomer **5**, and oligomers **8**, **9**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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