Syntheses and Circular Dichroism (CD) Spectra of Optically Active Polyoxazolines and Their Model Compounds

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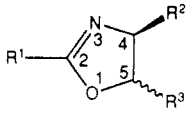
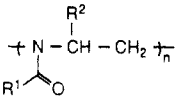
ABSTRACT: The optically active poly(*N*-acyl-1-alkylethylenimines) have been synthesized from the corresponding 2-oxazolines by ring-opening polymerization. The model compounds, from monomers through tetramers, have also been prepared. Comparative circular dichroism (CD) studies of these polymers and model compounds indicate that polymers and tetrameric model compounds have the same conformations as established from our molecular mechanics calculations.

Introduction

Optically active polyoxazolines represent a new class of mimetic structures of proteins. Since Bergmann[1] first reported 2-oxazoline derivative (**1a**) in 1923, the preparation, purification and polymerization of 2-oxazolines have been challenging problems. Before the pioneering works of Witte[2] and Saegusa[3] in the early 1970s, the preparation of oxazolines required either highly acidic[4] or basic[5] conditions which were not suitable for the preparation of optically active oxazolines. Although 2-oxazolines were prepared with mild conditions using a zinc[2] or silver[3] catalyst, the purification was difficult, yet critical for the polymerization. There are many optically active oxazolines known.[6-8] However, poly(*N*-formyl-1-methylethylenimine)[6,7] (**2**) is the only known optically active polyoxazoline, and the efforts aimed at elucidating the polymer conformations have not been fruitful. In our laboratories, molecular mechanics calculations were carried out for poly(*N*-acetyl-1-methylethylenimine) (n = 20) and its model compounds, monomer through tetramer.[9] The calculated structures of the polymer and tetramer are the same left-handed helices containing 14 residues/three turns with the identity period of 17.8 Å[10] (Figure 1). In order to study the structural properties of these new polymers, we have synthesized various optically active analogs of poly(*N*-acyl-1-methylethylenimine) and poly(*N*-acyl-1-benzylethylenimine) and their model compounds from monomers to tetramers. In this paper, we report the syntheses of 2-oxazolines and their polymerization. We also report on the preparation of corresponding model compounds. In addition, this paper contains circular dichroism (CD) spectra and a discussion of the conformational information for the polymer structures and their model compounds. The conformational studies of those polymers and model compounds using NMR are currently ongoing in our laboratories.





1a, R^1 = H, R^2 = H, R^3 = $CH_2OC(O)Ph$
b, R^1 = H, R^2 = CH_3, R^3 = H
c, R^1 = CH_3, R^2 = CH_3, R^3 = H
d, R^1 = H, R^2 = CH_2Ph, R^3 = H
e, R^1 = CH_3, R^2 = CH_2Ph, R^3 = H

2, R^1 = H, R^2 = CH_3
3, R^1 = CH_3, R^2 = CH_3
4, R^1 = H, R^2 = CH_2Ph
5, R^1 = CH_3, R^2 = CH_2Ph

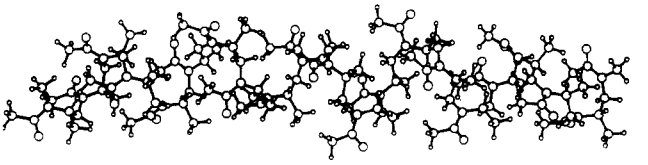


Figure 1. Preferred structure of poly(*N*-acetyl-1-methylethylenimine) (n = 20) established by conformational energy minimizations. The structure of the polymer is defined by a 14/3 left-handed helix with the identity period of 17.8 Å.

Experimental Section

Conformational Energy Calculations. Molecular mechanics calculations were carried out for poly(*N*-acetyl-1-methylethylenimine) and the monomer to tetramer model compounds employing the Discover force field program.[11] Conventional values of the bond lengths and bond angles were taken from the crystallographic data reported on ethylidene-*N*,*N*′-diacetamide[12] and the electron diffraction data reported on ethylenediamine[13] for the initiation of the iterative geometry optimization. Conformational energies were estimated as the sum of the nonbonded van der Waals interactions, the intrinsic torsional potentials, and the energy of deformation of bond lengths and bond angles. Parameters required for the description of the torsional potentials for the internal bond rotation are provided in the Discover program and used without modification. Various force constants defined in the valence force field scheme were also adopted as specified in the program.

Synthesis. 4-Methyl-2-oxazoline (1b). To a mixture of (*S*)-2-amino-1-propanol (7.5 g, 0.1 mol) and *tert*-butyl isocyanide (8.3 g, 0.1 mol) was added silver cyanide (0.67 g, 0.005 mol) under N_2. The resulting mixture was heated at 90 °C for 15 h and fractionally distilled. After collection of product containing portions, the mixtures were redistilled under reduced pressure with ion-exchange resin (Amberlite IRC-50) to remove small amounts of unreacted starting material and *tert*-butylamine as byproducts. The distillations were repeated until pure 4-methyl-2-oxazoline (**1b**) was obtained: yield 4.0 g (47%); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3 H, CH_3), 3.72 (dd, J = 8.5, 8.5 Hz, 1 H, C*H*H), 4.14 (m, 1 H, C*H*CH_3), 4.28 (dd, J = 8.5, 8.5 Hz, 1 H, CH*H*), 6.76 (s, 1 H, N=CH) ppm; $[\alpha]^{25}_D$ −148° (c = 1.0, EtOH); MS (+FAB) 86 ($[M + 1]^+$, M = C_4H_7NO).

Anal. Calcd for C_4H_7NO: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.17; H, 8.52; N, 16.29.

4-Benzyl-2-oxazoline (1d). To a mixture of (*S*)-2-amino-3-phenyl-1-propanol (7.6 g, 50 mmol) and *tert*-butyl isocyanide (4.15 g, 50 mmol) was added silver cyanide (0.34 g, 2.5 mmol) under N_2. The resulting mixture was heated at 90 °C for 15 h and fractionally distilled. After collection of product-containing fractions, the mixture was redistilled under reduced pressure with ion-exchange resin (Amberlite IRC-50) to remove small

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amounts of unreacted starting material and *tert*-butylamine byproduct. The distillations were repeated until pure 4-benzyl-2-oxazoline (**1d**) was obtained: yield 4.6 g (57%); ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, J = 6.5, 13.2 Hz, 1 H, C*H*HPh), 3.09 (dd, J = 6.5, 13.2 Hz, 1 H, CH*H*Ph), 3.91 (dd, J = 8.7, 8.7 Hz, 1 H, C*H*HO), 4.16 (dd, J = 8.7, 8.7 Hz, 1 H, CH*H*O), 4.39 (m, 1 H, NC*H*CH_2), 6.80 (s, 1 H, N=CH), 7.17–7.38 (m, 5 H, C_6H_5) ppm; $[\alpha]^{25}_D$ +74.4° (c = 1.0, EtOH); MS (+FAB) 162 ([M + 1]$^+$, M = $C_{10}H_{11}NO$).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.17; H, 7.06; N, 8.54.

***N*-(2-Hydroxy-1-methylethyl)acetamide (10a).** Acetic anhydride (30 mL) was added dropwise to (*S*)-2-amino-1-propanol (7.5 g, 0.1 mol) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. After evaporation of the excess acetic anhydride, the title compound **10a** was recrystallized (methanol–ether): yield 11.1 g (95%); R_f 0.20 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.7 Hz, 3 H, C*H*$_3$CH), 2.04 (s, 3 H, CH_3C=O), 3.58 (m, 1 H, C*H*HOH), 3.72 (m, 1 H, CH*H*OH), 4.10 (m, 1 H, C*H*CH_3), 5.43 (br s, 1 H, OH), 6.38 (br s, 1 H, NH) ppm.

***N*-(2-Hydroxy-1-benzylethyl)acetamide (10b).** (*S*)-2-Amino-3-phenyl-1-propanol (7.6 g, 50 mmol) was acetylated by the method described above to give compound **10b**: yield 8.55 g (88%); R_f 0.55 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H, CH_3), 2.87 (d, J = 6.9 Hz, 2 H, CH_2Ph), 3.18 (br s, 1 H, OH), 3.59 (m, 1 H, C*H*HOH), 3.66 (m, 1 H, CH*H*OH), 4.19 (m, 1 H, CH), 6.17 (br s, 1 H, NH), 7.20–7.36 (m, 5 H, C_6H_5) ppm.

***N*-(2-Chloro-1-methylethyl)acetamide (11a).** To a solution of *N*-(2-hydroxy-1-methylethyl)acetamide (**10a**) (10 g, 85.5 mmol) in *N*,*N*-dimethylformamide (DMF, 20 mL) was added thionyl chloride (6.24 mL, 85.5 mmol) dropwise at 0 °C. The resulting mixture was heated at 40–45 °C for 30 min and distilled under reduced pressure to give the titled compound **11a** as a colorless oil: yield 6.48 g (56%); R_f 0.39 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.7 Hz, 3 H, C*H*$_3$CH), 2.03 (s, 3 H, CH_3C=O), 3.58 (m, 1 H, C*H*HCl), 3.70 (m, 1 H, CH*H*Cl), 4.37 (m, 1 H, C*H*CH_3), 6.05 (br s, 1 H, NH) ppm.

***N*-(2-Chloro-1-benzylethyl)acetamide (11b).** *N*-(2-Hydroxy-1-benzylethyl)acetamide (**10b**) (8.0 g, 41.4 mmol) was chlorinated by the method described above to give compound **11b** as an oil: yield 5.52 g (63%); R_f 0.74 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3 H, CH_3C=O), 2.80 (d, J = 6.8 Hz, 2 H, CH_2Ph), 3.56 (m, 1 H, C*H*HCl), 3.71 (m, 1 H, CH*H*Cl), 4.23 (m, 1 H, CH), 6.09 (br s, 1 H, NH), 7.18–7.36 (m, 5 H, C_6H_5) ppm.

2,4-Dimethyl-2-oxazoline (1c). *N*-(2-chloro-1-methylethyl)-acetamide (**11a**) (5.5 g, 40.6 mmol) was added dropwise to a stirred suspension of sodium hydride (0.97 g, 40.6 mmol) in dry 1-methyl-2-pyrrolidinone (15 mL) under N_2 cooled in an ice bath. After the addition was completed, the mixture was distilled under reduced pressure and the product **1c** was collected in a trap cooled at −78 °C: yield 2.6 g (65%); ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H, C*H*$_3$CH), 1.95 (s, 3 H, CH_3C=N), 3.73 (dd, J = 8.7, 8.7 Hz, 1 H, C*H*H), 4.10 (m, 1 H, C*H*CH_3), 4.31 (dd, J = 8.7, 8.7 Hz, 1 H, CH*H*) ppm; $[\alpha]^{25}_D$ −130.4° (c = 2.4, MeOH); MS (+FAB) 100 ([M + 1]$^+$, M = C_5H_9NO).

Anal. Calcd for C_5H_9NO: C, 60.05; H, 9.15; N, 14.13. Found: C, 59.88; H, 9.49; N, 14.47.

4-Benzyl-2-methyl-2-oxazoline (1e). The compound **1e** was obtained by the same method described above using *N*-(2-chloro-1-benzylethyl)acetamide (**11b**) (5.0 g, 23.6 mmol) and sodium hydride (0.57 g, 23.6 mmol): yield 2.86 g (69%); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 1 H, CH_3C=N) 2.64 (dd, J = 6.7, 13.8 Hz, 1 H, C*H*HPh), 3.09 (dd, J = 6.7, 13.8 Hz, 1 H, CH*H*Ph), 3.93 (dd, J = 8.7, 8.7 Hz, 1 H, C*H*HO), 4.17 (dd, J = 8.7, 8.7 Hz, 1 H, CH*H*O), 4.36 (m, 1 H, CH), 7.19–7.32 (m, 5 H, C_6H_5) ppm; $[\alpha]^{25}_D$ −66.7° (c = 1.0, MeOH); MS (+FAB) 176 ([M + 1]$^+$, M = $C_{11}H_{13}NO$).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.26; N, 8.05.

Poly(*N*-formyl-1-methylethylenimine) (2). A mixture of 4-methyl-2-oxazolines (**1b**) (2.0 g, 23.5 mmol) and methyl *p*-toluenesulfonate (53 μL, 0.35 mmol, 0.015 equiv) was heated at 120 °C for 3 days in a sealed tube. As the polymerization progressed, the polymer layer, as a glasslike semisolid, grew from the bottom of the sealed tube. After the polymerization was finished, a small amount of methanol (3 mL) was added and the polymer precipitated as a white solid with the addition of ether. The degree of polymerization was about 60 on the basis of the ^{1}H NMR integration: yield 1.76 g (88%); $\eta_{sp/c}$ 0.22 (1.0 g/dL in water); ^{1}H NMR ($CDCl_3$) δ 1.22–1.43 (m, 3 H, CH_3), 3.11–4.32 (m, 3 H, $CHCH_2$), 7.20 (d, J = 6.5 Hz, 0.03 H, $^1/_2C_6H_4$), 7.73 (d, J = 6.5 Hz, 0.03 H, $^1/_2C_6H_4$), 7.80–8.25 (br m, 1 H, C(O)H) ppm; $[\alpha]^{25}_D$ + 130° (c = 1.0, MeOH).

Poly(*N*-formyl-1-benzylethylenimine) (4). The polymerization of 4-benzyl-2-oxazoline (**1d**) (2.0 g, 12.4 mmol) was conducted by the method described above using methyl *p*-toluenesulfonate (17.0 μL, 0.11 mmol, 0.009 equiv) as an initiator. The degree of polymerization was about 100 on the basis of the ^{1}H NMR integration: yield 1.71 g (85%); $\eta_{sp/c}$ 0.40 (1.0 g/dL in DMF); ^{1}H NMR ($CDCl_3$) δ 2.46–4.21 (m, 5 H, $CH(CH_2)_2$), 6.71–7.40 (m, 5 H, C_6H_5), 7.70 (d, J = 6.5 Hz, 0.02 H, $^1/_2C_6H_4$), 7.81–8.25 (m, 1 H, C(O)H) ppm; $[\alpha]^{25}_D$ +16.5° (c = 1.0, CF_3CH_2OH).

Poly(*N*-acetyl-1-methylethylenimine) (3). The polymerization of 2,4-dimethyl-2-oxazoline (**1c**) (2.0 g, 20 mmol) was conducted by the method described above using methyl *p*-toluenesulfonate (20 μL, 0.13 mmol, 0.0067 equiv) as an initiator. The degree of polymerization was about 150 on the basis of the ^{1}H NMR integration: yield 1.83 g (92%); $\eta_{sp/c}$ 0.44 (1.0 g/dL in water); ^{1}H NMR ($CDCl_3$) δ 1.12–1.48 (m, 3 H, $CHCH_3$), 1.95–2.34 (m, 3 H, $C(O)CH_3$), 2.93–4.65 (m, 3 H, $CHCH_2$), 7.17 (d, J = 6.5 Hz, 0.013 H, $^1/_2C_6H_4$), 7.72 (d, J = 6.5 Hz, 0.013 H, $^1/_2C_6H_4$) ppm; $[\alpha]^{25}_D$ +139.5° (c = 1.4, MeOH).

Poly(*N*-acetyl-1-benzylethylenimine) (5). The polymerization of 4-benzyl-2-methyl-2-oxazoline (**1e**) (2.0 g, 11.4 mmol) was conducted by the method described above using methyl *p*-toluenesulfonate (35 μL, 0.23 mmol, 0.02 equiv) as an initiator. The degree of polymerization was about 50 on the basis of the ^{1}H NMR integration: yield 1.69 (84%); $\eta_{sp/c}$ 0.19 (1.0 g/dL in DMF); ^{1}H NMR ($CDCl_3$) δ 1.95–3.92 (m, 8 H, $CH(CH_2)_2$ and CH_3), 6.71–7.40 (m, 5 H, C_6H_5), 7.74 (d, 0.04 H, $^1/_2C_6H_4$) ppm; $[\alpha]^{25}_D$ −22.7° (c = 1.0, CF_3CH_2OH).

***N*-(2-Butyl)acetamide (12b).** Acetic anhydride (5 mL) was added dropwise to (*S*)-2-butylamine (0.5 g, 6.84 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. After evaporation of the excess acetic anhydride, the residue was purified by flash column chromatography: yield 756 mg (96%); R_f 0.36 (3% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.13 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.44 (m, 2 H, CH_2), 1.98 (s, 3 H, $C(O)CH_3$), 3.92 (m, 1 H, CH), 5.58 (br s, 1 H, NH) ppm.

***N*-(2-Butyl)formamide (12a).** A mixture of acetic anhydride (2.5 mL) and formic acid (2.5 mL) was added dropwise to (*S*)-2-butylamine (0.5 g, 6.84 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. After removal of the solvent, the residue was purified by column chromatography: yield 600 mg (87%); R_f 0.29 (3% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.19 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.40 (m, 2 H, CH_2), 3.76 (m, 1 H, C*H*CH_3), 5.95 (br s, 1 H, NH), 8.03 (s, 1 H, C(O)H) ppm.

***N*-(2-Butyl)-*N*-methylacetamide (6b).** *N*-(2-Butyl)acetamide (**12b**) (700 mg, 6.08 mmol) was dissolved in THF (5 mL), and the solution was cooled to 0 °C under N_2. After cessation of the bubbling that was caused by the addition of sodium hydride (150 mg, 6.25 mmol), iodomethane (3.0 mL, 48.2 mmol) was added slowly to the suspension. The reaction mixture was stirred for 24 h. After addition of water (0.5 mL), the solid material was removed by filtration through a Celite bed. The solvent was removed and the oily residue was partitioned between ether (10 mL) and water (20 mL). The ether layer was washed with aqueous $NaHCO_3$ solution. The combined aqueous extracts were acidified to pH 2 with 6 N aqueous HCl solution at 0 °C. The product was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with saturated aqueous NaCl solution (2 × 10 mL), 5% aqueous $Na_2S_2O_3$ solution, (3 × 10 mL), and saturated aqueous NaCl solution (2 × 10 mL). This solution was dried over Na_2SO_4, and the solvent was evaporated to give a pale yellow oil. This oily product was purified by column chromatography to give a 1:2 mixture of *cis* and *trans* isomers of **6b**: yield 487 mg (62%); R_f 0.56 (3% methanol–chloroform); ^{1}H NMR for cis isomer of **6b** ($(CF_3)_2CDOD$) δ 0.86 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.24 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.54 (m, 2 H, CH_2), 2.14 (s, 3 H, $CH_3C(O)$), 2.88 (s, 3 H, CH_3N), 4.55 (m, 1 H, CH) ppm. ^{1}H NMR for

trans isomer of **6b** ($(CF_3)_2CDOD$): δ 0.90 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.13 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.62 (m, 2 H, CH_2), 2.18 (s, 3 H, $CH_3C(O)$), 2.82 (s, 3 H, CH_3N), 3.84 (m, 1 H, CH) ppm. The ^1H NMR assignments were confirmed by the corresponding COSY experiment. MS (+FAB) 130 ($[M + 1]^+$, M = $C_7H_{15}NO$).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.35; H, 11.62; N, 10.86.

***N*-(2-Butyl)-*N*-methylformamide (6a).** *N*-(2-Butyl)formamide (**12a**) (500 mg, 4.94 mmol) was methylated by the method described above. The residue was purified by column chromatography to give a 1:4 mixture of cis and trans isomers of **6a**: yield 336 mg (59%); R_f 0.49 (3% methanol–chloroform); ^1H NMR for cis isomer of **6a** ($(CF_3)_2CDOD$) δ 0.90 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.20 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.64 (m, 2 H, CH_2), 2.90 (s, 3 H, CH_3N), 4.40 (m, 1 H, CH), 7.94 (s, 1 H, C(O)H) ppm. ^1H NMR for trans isomer of **6a** ($(CF_3)_2CDOD$): δ 0.90 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.30 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.64 (m, 2 H, CH_2), 2.82 (s, 3 H, CH_3N), 3.45 (m, 1 H, CH), 7.98 (s, 1 H, C(O)H) ppm. The ^1H NMR assignments were confirmed by the corresponding COSY experiment. MS (+FAB) 116 ($[M + 1]^+$, M = $C_6H_{13}NO$).

Anal. Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.37; N, 12.16. Found: C, 62.86; H, 11.04, N, 11.99.

Boc(NMe)AlaOH (13a). The methylation of BocAlaOH (1.25 g, 6.6 mmol) was carried out by the method described above. The oily residue was purified by flash column chromatography to give the title compound **13a**: yield 0.82 g (61%); R_f 0.51 (chloroform–methanol–acetic acid 85:10:5); mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, $CHCH_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 2.86 (s, 3 H, NCH_3), 4.48 (m, 0.32 H, *cis*-CH), 4.80 (m, 0.68 H, *trans*-CH) ppm.

Boc(NMe)PheOH (13b). The title compound was obtained by the method described above, employing BocPheOH (2.0 g, 7.54 mmol), NaH (181 mg, 7.54 mmol), and iodomethane (3.75 mL, 60.3 mmol). The oily residue was purified by flash column chromatography: yield 1.37 g (65%); R_f 0.88 (chloroform–methanol–acetic acid 85:10:5); ^1H NMR ($CDCl_3$) δ 1.33 (s, 4.27 H, *cis*-$C(CH_3)_3$), 1.40 (s, 4.73 H, *trans*-$C(CH_3)_3$), 2.68 (s, 1.42 H, *cis*-NCH_3), 2.76 (s, 1.58 H, *trans*-NCH_3), 3.10 and 3.32 (2 m, 2 H, *cis*- and *trans*-CH_2), 4.64 (m, 0.47 H, *cis*-CH), 4.80 (m, 0.53 H, *trans*-CH) ppm.

General Procedure for the Peptide Bond Coupling Reaction with EDC. A solution of an amino terminal protected and a carboxyl terminal protected amino acid or peptide fragment in DMF (0.1–1.0 M) was cooled to −10 °C. 1-Hydroxybenzotriazole (HOBt, 1.2 equiv) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC, 1.3 equiv) were added, and the pH of the reaction mixture was adjusted to 7 with 4-methylmorpholine. Stirring was continued for 1 h at −10 °C and 2 h or longer at room temperature. After completion of the reaction and checked by TLC, solvent was removed under reduced pressure. The residue was dissolved in chloroform and successively washed with saturated aqueous $NaHCO_3$ solution (two or three times), saturated aqueous NaCl solution, 0.5 N aqueous HCl solution or 5% aqueous citric acid solution, and saturated aqueous NaCl solution. The volume of each washing solution was approximately $^1/_{10}$th of the volume of the chloroform layer. After the washed organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure to give an oil or powder. This crude product was recrystallized (ethyl acetate–hexane) or purified by flash column chromatography to obtain pure product.

General Procedure for Deprotection of the *tert*-Butyloxycarbonyl (Boc) Group. A Boc-protected amino acid or peptide fragment was dissolved in dichloromethane and trifluoroacetic acid (1:1 v/v) while the temperature was maintained at 0 °C with an ice bath. The volume of trifluoroacetic acid corresponded to 20–30 equiv of the starting materials. After stirring for 10 min, the ice bath was removed and stirring was continued at room temperature until all the starting material was consumed. Dichloromethane and trifluoroacetic acid were removed under reduced pressure. The residue was recrystallized (methanol–ether) to give the TFA salt of the amino acid terminal deprotected peptide.

Boc(NMe)AlaNHCH$(CH_3)_2$ (14a). The coupling between Boc(NMe)AlaOH (2.0 g, 9.84 mmol) and 2-propylamine (870 mg, 14.71 mmol) was achieved by the method described in the general coupling procedure employing HOBt (1.60 g, 11.84 mmol) and EDC (2.45 g, 12.78 mmol). The crude material was purified by flash column chromatography using methanol and chloroform as an eluent to give pure title compound: yield 2.26 g (94%); R_f 0.33 (5% methanol–chloroform); ^1H NMR ($CDCl_3$) δ 1.14 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.36 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 2.78 (s, 3 H, NCH_3), 4.06 (m, 1 H, $CH(CH_3)_2$), 4.60 (q, J = 6.8 Hz, 1 H, $CHCH_3$), 5.93 (br s, 1 H, NH) ppm.

Boc(NMe)PheNHCH$(CH_3)_2$ (14b). The coupling between Boc(NMe)PheOH (2.0 g, 7.16 mmol) and 2-propylamine (635 mg, 10.74 mmol) was achieved by the method described in the general coupling procedure employing HOBt (1.16 g, 8.59 mmol) and EDC (1.37 g, 10.14 mmol). The crude residue was purified by flash column chromatography to give a 1:1 mixture of cis and trans isomers of **14b**: yield 2.08 g (90%); R_f 0.50 (5% methanol–chloroform); ^1H NMR ($CDCl_3$) δ 1.12 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.31, 1.40 (2 s, 9 H, $C(CH_3)_3$), 2.77 (br s, 3 H, NCH_3), 2.91, 3.38 (2 m, 2 H, CH_2Ph), 4.02 (m, 1 H, $CH(CH_3)_2$), 4.63, 4.82 (2 m, 1 H, CHC(O)), 5.65, 5.97 (2 br s, 1 H, NH), 7.12–7.34 (m, 5 H, C_6H_5) ppm.

(NMe)AlaNHCH$(CH_3)_2$ (15a). The Boc group was removed by the method described in the general deprotection procedure from Boc(NMe)AlaNHCH$(CH_3)_2$ (**14a**) (2.0 g, 8.19 mmol) and the crude compound was extracted with chloroform from the basic aqueous solution. After drying over Na_2SO_4, solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give pure title compound **15a**: yield 920 mg (78%); R_f 0.22 (10% methanol–chloroform); ^1H NMR ($CDCl_3$) δ 1.15 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.28 (d, J = 6.8 HZ, 3 H, $CHCH_3$), 2.40 (s, 4 H, CH_3N and CH_3NH), 3.09 (q, J = 6.8 Hz, 1 H, $CHCH_3$), 4.05 (m, 1 H, $CH(CH_3)_2$), 7.04 (br s, 1 H, C(O)NH) ppm.

(NMe)PheNHCH$(CH_3)_2$ (15b). The Boc group was removed from Boc(NMe)AlaNHCH$(CH_3)_2$ (**14b**) (2.0 g, 6.24 mmol) by the method described in the general deprotection procedure. The crude product was purified by flash column chromatography to give pure title compound **15b**: yield 1.14 g (83%); R_f 0.48 (10% methanol–chloroform); ^1H NMR ($CDCl_3$) δ 1.14 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.66 (br s, 1 H, CH_3NH), 2.29 (s, 3 H, CH_3NH), 2.72 (dd, J = 6.7, 13.8 Hz, 1 H, CHHPh), 3.20 (m, 2 H, CHHPh and $CHCH_2$), 4.08 (m, 1 H, $CH(CH_3)_2$), 6.92 (br s, 1 H, C(O)NH), 7.21–7.35 (m, 5 H, C_6H_5) ppm.

(3*S*)-2,5-Diaza-3,6-dimethylheptane (16a). To a solution of 1.0 M borane in tetrahydrofuran (15 mL) under N_2 was added (NMe)AlaNHCH$(CH_3)_2$ (**15a**) (800 mg, 5.55 mmol) in THF (5 mL) dropwise, and the temperature was kept at approximately 0 °C. The colorless solution was then heated to reflux for 2 h. The reaction mixture was cooled to room temperature, and a 6 N aqueous HCl solution (5 mL) was added. After the tetrahydrofuran was removed under reduced pressure, NaOH pellets were added to saturate the aqueous phase and the crude product was extracted with chloroform (3 × 10 mL). The product was purified by flash column chromatography to furnish the title compound **16a** as an oil: yield 390 mg (59%); ^1H NMR ($CDCl_3$) δ 1.18 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.21 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 2.46 (s, 3 H, CH_3N), 2.54 (m, 1 H, CHH), 2.72 (m, 2 H, CHH and $CHCH_3$), 2.83 (m, 1 H, $CH(CH_3)_2$), 3.42 (br s, 2 H, 2 × NH) ppm.

(3*S*)-2,5-Diaza-3-benzyl-6-methylheptane (16b). The reduction of (NMe)PheNHCH$(CH_3)_2$ (**15b**) (1.0 g, 4.54 mmol) was achieved by the method described above. The crude product was purified by flash column chromatography to give the title compound: yield 645 mg (69%); ^1H NMR ($CDCl_3$) δ 1.17 (2 d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$), 1.99 (br s, 2 H, 2 × NH), 2.50 (s, 3 H, CH_3N), 2.67 (m, 1 H, CHHPh), 2.78–2.89 (m, 2 H, CH_2N), 2.93–3.07 (m, 2 H, CHHPh and $CHCH_2$), 3.14 (m, 1 H, $CH(CH_3)_2$), 7.20–7.38 (m, 5 H, C_6H_5) ppm.

(3*S*)-2,5-Diacetyl-2,5-diaza-3,6-dimethylheptane (7b). Acetic anhydride (5 mL) was added dropwise to (3*S*)-2,5-diaza-3,6-dimethylheptane (**16a**) (150 mg, 1.15 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After evaporation of excess acetic anhydride, the crude product was purified by column chromatography to give the pure title compound: yield 210 mg (85%); R_f 0.37 (10% methanol–chloroform); ^1H NMR ($CDCl_3$) δ 1.15–1.37 (m, 9 H, $CHCH_3$ and

$CH(CH_3)_2$), 2.07–2.16 (m, 6 H, 2 × $C(O)CH_3$), 2.84–2.97 (m, 3 H, CH_3N), 2.99, 3.11, 3.26, 3.57 (4 m, 2 H, CH_2), 4.03 (m, 1 H, $CH(CH_3)_2$), 4.25, 4.54, 4.80, 4.87 (4 m, 1 H, $CHCH_3$) ppm; MS (+FAB) 215 ([M + 1]$^+$, M = $C_{11}H_{22}N_2O_2$).

Anal. Calcd for $C_{11}H_{22}N_2O_2$: C, 61.64; H, 10.35; N, 13.07. Found: C, 61.38; H, 10.61; N, 12.72.

(3*S*)-2,5-Diacetyl-2,5-diaza-3-benzyl-6-methylheptane (7a). Acetylation was conducted with (3*S*)-2,5-diaza-3-benzyl-6-methylheptane (**16b**) (250 mg, 1.21 mmol) using the method described above, and the crude product was purified by preparative thin-layer chromatography (PTLC): yield 310 mg (88%); R_f 0.60 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.03–1.24 (m, 6 H, $CH(CH_3)_2$), 1.76–2.22 (m, 6 H, 2 × $C(O)CH_3$), 2.75–5.12 (m, 9 H, $CH(CH_3)_2$, $CH(CH_2)_2$ and CH_3N), 7.14–7.22 (m, 5 H, C_6H_5) ppm; MS (+FAB) 291 ([M + 1]$^+$, M = $C_{17}H_{26}N_2O_2$).

Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.03; N, 9.65. Found: C, 70.26; H, 9.08; N, 9.49.

(3*S*)-2,5-Diformyl-2,5-diaza-3,6-dimethylheptane (7d). A mixture of acetic anhydride (2.5 mL) and formic acid (2.5 mL) was added dropwise to (3*S*)-2,5-diaza-3,6-dimethylheptane (**16a**) (150 mg, 1.15 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After removal of solvent, the residue was purified by column chromatography to give the title compound: yield 152 mg (71%); R_f 0.28 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.20–1.41 (m, 9 H, $CHCH_3$ and $CH(CH_3)_2$), 2.86–3.02 (m, 3 H, CH_3N), 3.10–4.74 (m, 4 H, $CHCH_3$, $CH(CH_3)_2$, and CH_2), 7.90–8.19 (m, 2 H, 2 × C(O)H) ppm; MS (+FAB) 187 ([M + 1]$^+$, M = $C_9H_{18}N_2O_2$).

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.83; H, 10.01; N, 15.27.

(3*S*)-2,5-Diformyl-2,5-diaza-3-benzyl-6-methylheptane (7c). Formylation was carried out with (3*S*)-2,5-diaza-3-benzyl-6-methylheptane (**16b**) (250 mg, 1.21 mmol) by the method described above, and the residue was purified by PTLC: yield 261 mg (82%); R_f 0.52 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.13–1.32 (m, 6 H, $CH(CH_3)_2$), 2.77–4.92 (m, 9 H, CH_3N, $CH(CH_2)_2$ and $CH(CH_3)_2$), 7.10–7.37 (m, 5 H, C_6H_5), 7.77–8.26 (m, 2 H, 2 × C(O)H) ppm; MS (+FAB) 263 ([M + 1]$^+$, M = $C_{15}H_{22}N_2O_2$).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.74; H, 8.55; N, 10.89.

BocAlaNHCH(CH$_3$)$_2$ (17a). The coupling with BocAlaOH (5.0 g, 26.4 mmol) and 2-propylamine (2.8 g, 47.4 mmol) was achieved by the method described in the general coupling procedure employing HOBt (4.7 g, 34.8 mmol) and EDC (7.6 g, 39.6 mmol). After recrystallization from ethyl acetate–hexane, white crystals were collected: 5.7 g (94%); R_f 0.45 (10% methanol–hexane); ^{1}H NMR ($CDCl_3$) δ 1.16 (2 d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$), 1.35 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.45 (s, 9 H, $C(CH_3)_3$), 4.03–4.18 (m, 2 H, 2 × CH), 5.11, 6.12 (2 br s, 2 H, 2 × NH) ppm; MS (+FAB) 231 ([M + 1]$^+$, M = $C_{11}H_{22}N_2O_3$).

Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.17. Found: C, 57.56; H, 9.48; N, 11.82.

BocPheNHCH(CH$_3$)$_2$ (17b). The coupling between BocPheOH (5.0 g, 18.8 mmol) and 2-propylamine (2.0 g, 33.8 mmol) was achieved by the method described in the general procedure employing HOBt (3.4 g, 25.2 mmol) and EDC (5.5 g, 28.7 mmol). After recrystallization from ethyl acetate–hexane, white crystals were collected: yield 5.37 g (93%); R_f 0.62 (10% methanol–hexane); ^{1}H NMR ($CDCl_3$) δ 0.95, 1.04 (2 d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$), 1.43 (s, 9 H, $C(CH_3)_3$), 2.95–3.13 (m, 2 H, CH_2Ph), 3.97, 4.23 (2 m, 2 H, 2 × CH), 5.20, 5.51 (2 br s, 2 H, 2 × NH), 7.21–7.36 (m, 5 H, C_6H_5) ppm; MS (+FAB) 307 ([M + 1]$^+$, M = $C_{17}H_{26}N_2O_3$).

Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.91; H, 8.74; N, 9.30.

(NMe)AlaAlaNHCH(CH$_3$)$_2$ (18a). After removal of the Boc group from BocAlaNHCH(CH_3)$_2$ (**17a**) (2.3 g, 10 mmol) by the general deprotection procedure, the coupling reaction with Boc-(NMe)AlaOH (**13a**) (2.0 g, 10 mmol) was carried out using HOBt (1.62 g, 12 mmol) and EDC (2.5 g, 13 mmol). After workup, the Boc group of Boc(NMe)AlaAlaNHCH(CH_3)$_2$ was removed and the residue was purified by recrystallization to give the titled compound as a TFA salt: yield 2.65 g (81%); ^{1}H NMR (DMSO-d_6) δ 1.01 (2 d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$), 1.22, 1.37 (2 d, J = 7.0 Hz, 6 H, 2 × $CHCH_3$), 2.52 (s, 3 H, NCH_3), 3.60, 3.82, 4.26 (3 m, 3 H, 3 × CH), 7.86, 8.69 (2 d, J = 7.6 Hz, 2 × NH), 8.83, 9.02 (2 br s, 2 H, NH_2) ppm.

(NMe)PhePheNHCH(CH$_3$)$_2$ (18b). After removal of the Boc group from BocPheNHCH(CH_3)$_2$ (**17b**) (3.06 g, 10 mmol) by the general deprotection procedure, the coupling reaction with Boc-(NMe)PheOH (**13b**) (2.79 g, 10 mmol) was carried out using HOBt (1.62 g, 12 mmol) and EDC (2.5 g, 13 mmol). After workup, the Boc group of Boc(NMe)PhePheNHCH(CH_3)$_2$ was removed and the residue was purified by recrystallization to give the title compound as a TFA salt: yield 3.83 g (80%); ^{1}H NMR (DMSO-d_6) δ 0.97, 1.06 (2 d, J = 6.6 Hz, 6 H, $CH(CH_3)_2$), 2.71–2.97 (m, 4 H, 2 × CH_2Ph), 3.71–3.85, 4.62 (2 m, 3 H, 3 × CH), 7.12–7.29 (m, 10 H, 2 × C_6H_5), 7.93, 8.66 (2 d, J = 7.5 Hz, 2 H, 2 × NH), 8.84 (br s, 2 H, NH_2) ppm.

(3*S*,6*S*)-2,5,8-Triaza-3,6,9-trimethyldecane (19a). To a solution of 1.0 M borane in THF (30 mL) under N_2 atmosphere was added (NMe)AlaAlaNHCH(CH_3)$_2$ (**18a**) (2.3 g, 7.0 mmol) in THF (10 mL) dropwise, and the temperature was kept at approximately 0 °C. The colorless solution was then heated to reflux for 12 h. The reaction mixture was cooled to room temperature, and 6 N aqueous HCl solution (10 mL) was added. After the solvent was removed under reduced pressure, NaOH pellets were added to saturate the aqueous phase and the product was extracted with chloroform (3 × 30 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was not further purified but used for the following reactions: crude product yield 680 mg (52%).

(3*S*,6*S*)-3,6-Dibenzyl-9-methyl-2,5,8-triazadecane (19b). The reduction of (NMe)PhePheNHCH(CH_3)$_2$ (**18b**) (3.5 g, 7.28 mmol) was achieved by the method described above. The crude product was not further purified but used for the following reactions: crude product yield 1.48 g (60%).

(3*S*,6*S*)-2,5,8-Triacetyl-2,5,8-triaza-3,6,9-trimethyldecane (8b). Acetic anhydride (5 mL) was added dropwise to crude (3*S*,6*S*)-2,5,8-triaza-3,6,9-trimethyldecane (**19a**) (300 mg, 1.60 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After evaporation of excess acetic anhydride, the crude product was purified by flash column chromatography: yield 331 mg (66%); R_f 0.34 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.06–1.47 (m, 12 H, 2 × CH_2CHCH_3 and $CH(CH_3)_2$) 2.02–2.34 (m, 9 H, 3 × $C(O)CH_3$), 2.78–4.92 (m, 10 H, CH_3N, $CH(CH_3)_2$ and 2 × CH_3CHCH_2) ppm; MS (+FAB) 314 ([M + 1]$^+$, M = $C_{16}H_{31}N_3O_3$).

Anal. Calcd for $C_{16}H_{31}N_3O_3$: C, 61.31; H, 9.97; N, 13.41. Found: C, 61.67; H, 10.06; N, 13.11.

(3*S*,6*S*)-3,6-Dibenzyl-9-methyl-2,5,8-triacetyl-2,5,8-triazadecane (8d). Acetylation was conducted with (3*S*,6*S*)-3,6-dibenzyl-9-methyl-2,5,8-triazadecane (500 mg, 1.47 mmol) (**19b**) by the method described above, and the crude product was purified by PTLC: yield 425 mg (62%); R_f 0.54 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.06–1.38 (m, 6 H, $CH(CH_3)_2$), 1.62–2.25 (m, 9 H, 3 × $C(O)CH_3$), 2.53–4.82 (m, 14 H, $CH(CH_3)_2$, CH_3N, and 2 × $CH(CH_2)_2$), 6.94–7.39 (m, 10 H, 2 × C_6H_5) ppm; MS (+FAB) 466 ([M + 1]^1, M = $C_{28}H_{39}N_3O_3$).

Anal. Calcd for $C_{28}H_{39}N_3O_3$: C, 72.22; H, 8.44; N, 9.02. Found: C, 72.35; H, 8.40; N, 8.89.

(3*S*,6*S*)-2,5,8-Triaza-2,5,8-triformyl-3,6,9-trimethyldecane (8a). A mixture of acetic anhydride (2.5 mL) and formic acid (2.5 mL) was added dropwise to (3*S*,6*S*)-2,5,8-triaza-3,6,9-trimethyldecane (**19a**) (300 mg, 1.60 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. After removal of solvent under reduced pressure, the residue was purified by flash column chromatography: yield 260 mg (60%); R_f 0.25 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.09–1.48 (m, 12 H, $CH(CH_3)_2$ and 2 × CH_2CHCH_3) 2.78–2.98 (m, 3 H, CH_3N), 3.08–4.05 (m, 7 H, 2 × CH_3CHCH_2 and $CH(CH_3)_2$), 7.82–8.28 (m, 3 H, C(O)H) ppm; MS (+FAB) 272 ([M + 1]$^+$, M = $C_{13}H_{25}N_3O_3$).

Anal. Calcd for $C_{13}H_{25}N_3O_3$: C, 57.54; H, 9.29; N, 15.49. Found: C, 57.87; H, 9.41; N, 15.44.

(3*S*,6*S*)-3,6-Dibenzyl-9-methyl-2,5,8-triformyl-2,5,8-triazadecane (8c). Formylation was achieved with (3*S*,6*S*)-3,6-dibenzyl-9-methyl-2,5,8-triazadecane (**19b**) (500 mg, 1.47 mmol) by the method described above, and the residue was purified by PTLC: yield 337 mg (54%); R_f 0.48 (10% methanol–chloroform);

^{1}H NMR ($CDCl_3$) δ 1.04–1.36 (m, 6 H, $CH(CH_3)_2$), 2.34–4.12 (m, 14 H, CH_3N, $CH(CH_3)_2$, and 2 × $CH(CH_2)_2$), 7.02–7.43 (m, 10 H, 2 × C_6H_5), 7.77–8.25 (m, 3 H, 3 × C(O)H) ppm; MS (+FAB) 424 ([M + 1]$^+$, M = $C_{25}H_{33}N_3O_3$).

Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 71.03; H, 7.66; N, 9.75.

Boc(NMe)AlaAlaOH (20a). The coupling between Boc(NMe)AlaOH (**13a**) (1.0 g, 4.92 mmol) and the HCl salt of AlaOBzl (1.06 g, 4.92 mmol) was accomplished by the general method employing HOBt (0.8 g, 5.92 mmol) and EDC (1.25 g, 6.52 mmol) to obtain the Boc(NMe)AlaAlaOBzl compound: ^{1}H NMR ($CDCl_3$) δ 1.28, 1.34 (2 d, J = 7.0 Hz, 6 H, 2 × CH_3), 1.48 (s, 9 H, $CH(CH_3)_3$), 2.78 (s, 3 H, NCH_3), 4.60, 5.17 (2 m, 2 H, 2 × CH), 6.10 (br s, 1 H, NH), 7.27–7.37 (m, 5 H, C_6H_5) ppm. To remove the benzyl protecting group, crude Boc(NMe)AlaAlaOBzl was dissolved in 5% acetic acid–methanol (10 mL) containing 10% Pd/C as a catalyst. The reaction mixture was stirred for 12 h under H_2. The catalyst was removed by filtration through a Celite bed, and the solvent was removed under reduced pressure. The resulting oil was purified by flash column chromatography to give the title compound: yield 1.0 g (74%); R_f 0.26 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.32, 1.38 (2 d, J = 7.0 Hz, 6 H, 2 × CH_3), 1.53 (s, 9 H, $C(CH_3)_3$), 2.80 (s, 3 H, NCH_3), 4.44, 4.65 (2 m, 2 H, 2 × CH), 7.09 (br s, 1 H, NH), 9.88 (br s, 1 H, C(O)OH) ppm; MS (+FAB) 275 ([M + 1]$^+$, M = $C_{12}H_{22}N_2O_5$); HRMS (+FAB) 275.1599 (calculated for $C_{12}H_{23}N_2O_5$, 275.1607).

Boc(NMe)PhePheOH (20b). The coupling between Boc(NMe)PheOH (**13b**) (1.0 g, 3.58 mmol) and PheOBzl p-tosylate salt (1.53 g, 3.58 mmol), and the hydrogenolysis were conducted by the method described above: yield 1.05 g (69%); R_f 0.52 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.16, 1.24 (2 br s, 9 H, $C(CH_3)_3$), 2.33, 2.46 (2 br s, CH_3N), 2.78, 3.05, 3.33 (3 m, 4 H, 2 × CH_2Ph), 4.00–4.21 (m, 2 H, 2 × CH), 6.76 (br s, 1 H, NH), 7.08–7.25 (m, 10 H, 2 × C_6H_5) ppm; MS (+FAB) 427 ([M + 1]$^+$, M = $C_{24}H_{30}N_2O_5$); HRMS (+FAB) 427.2249 (calculated for $C_{24}H_{31}N_2O_5$, 427.2233).

AlaAlaNHCH(CH$_3$)$_2$ (21a). After the Boc group was removed from BocAlaNHCH(CH_3)$_2$ (**17a**) (2.0 g, 8.70 mmol) by the general procedure, the coupling reaction was carried out using BocAlaOH (1.65 g, 8.72 mmol), HOBt (1.41 g, 10.44 mmol), and EDC (2.24 g, 11.68 mmol). After workup, the Boc group of BocAlaAlaNHCH(CH_3)$_2$ was removed by the general method. The residue was purified by recrystallization to give the title compound as a TFA salt: yield 1.93 g (72%); ^{1}H NMR (DMSO-d_6) δ 1.03, 1.05 (2 d, J = 6.2 Hz, 6 H, $CH(CH_3)_2$), 1.21, 1.32 (2 d, J = 7.0 Hz, 6 H, 2 × $CHCH_3$), 3.79–3.87 (m, 2 H, 2 × CH), 4.27 (m, 1 H, CH), 7.84 (d, J = 7.5 Hz, 1 H, C(O)NH), 8.04 (br s, 3 H, NH_3), 8.49 (d, J = 7.5 Hz, 1 H, C(O)NH) ppm; MS (+FAB) 202 ([M − TFA + 1]$^+$, M = $C_{11}H_{20}N_3O_4F_3$, TFA = $C_2F_3HO_2$).

Anal. Calcd for $C_{11}H_{20}N_3O_4F_3$: C, 41.90; H, 6.39; N, 13.33. Found: C, 42.12; H, 6.38; N, 13.33.

BocPhePheNHCH(CH$_3$)$_2$ (21b). After the Boc group was removed from BocPheNHCH(CH_3)$_2$ (**17b**) (2.0 g, 6.54 mmol) by the general procedure, the coupling reaction was carried out using BocPheOH (1.74 g, 6.56 mmol), HOBt (1.06 g, 7.85 mmol), and EDC (1.75 g, 9.13 mmol). After workup, the residue was purified by recrystallization to give the title compound: yield 2.20 (75%); R_f 0.53 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.00 (2 d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$), 1.31 (s, 9 H, $C(CH_3)_3$), 2.80, 3.04, 3.26 (3 m, 4 H, 2 × CH_2Ph), 3.95, 4.27, 4.56 (3 m, 3 H, 3 × CH), 4.78 (d, J = 5.4 Hz, 1 H, OC(O)NH), 5.86, 6.36 (2 br s, 2 H, 2 × NH), 7.16–7.36 (m, 10 H, 2 × C_6H_5) ppm; MS (+FAB) 454 ([M + 1]$^+$, M = $C_{26}H_{35}N_3O_4$).

Anal. Calcd for $C_{26}H_{35}N_3O_4$: C, 68.85; H, 7.78; N, 9.26. Found: C, 69.09; H, 7.83; N, 9.27.

(NMe)AlaAlaAlaAlaNHCH(CH$_3$)$_2$ (22a). The coupling between Boc(NMe)AlaAlaOH (**20a**) (900 mg, 3.28 mmol) and AlaAlaNHCH(CH_3)$_2$ (**21a**) (660 mg, 3.28 mmol) was achieved by the general method employing HOBt (530 mg, 3.92 mmol) and EDC (880 mg, 4.59 mmol). After workup, the Boc group was removed by the general method. The residue was purified by recrystallization, and the product was obtained as a TFA salt: yield 1.20 g (79%); ^{1}H NMR (DMSO-d_6) δ 1.03, 1.04 (2 d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$), 1.16, 1.20, 1.26, 1.35 (4 d, J = 7.2 Hz, 12 H, $CHCH_3$), 2.50 (s, 3 H, NCH_3), 3.71–3.88 (m, 2 H, 2 × CH), 4.15–4.29 (m, 2 H, 2 × CH), 4.38 (m, 1 H, CH), 7.65, 7.81, 8.14, 8.67 (4 d, J = 7.8 Hz, 4 × NH), 8.75 (br s, 2 H, NH_3) ppm; MS (+FAB) 358 ([M − TFA + 1]$^+$, M = $C_{18}H_{32}N_5O_6F_3$, TFA = $C_2F_3HO_2$).

Anal. Calcd for $C_{18}H_{32}N_5O_6F_3$: C, 45.85; H, 6.84; N, 14.86. Found: C, 45.53; H, 6.78; N, 14.59.

(NMe)PhePhePhePheNHCH(CH$_3$)$_2$ (22b). After the Boc group was removed from BocPhePheNHCH(CH_3)$_2$ (**21b**) (0.96 g, 2.11 mmol) by the general deprotection method, the coupling with Boc(NMe)PhePheOH (**20b**) (0.90 g, 2.11 mmol) was achieved. The coupling agents HOBt (350 mg, 2.59 mmol) and EDC (570 mg, 2.97 mmol) were used. After workup, the Boc group was removed by the general method, the residue was purified by recrystallization, and the product was obtained as a TFA salt: yield 1.24 g (76%); ^{1}H NMR (DMSO-d_6) δ 0.91, 1.02 (2 d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$), 2.50–3.05 (m, 11 H, NCH_3 and 4 × CH_2Ph), 3.74–3.83 (m, 2 H, 2 × CH), 4.46–4.59 (m, 2 H, 2 × CH), 4.75 (m, 1 H, CH), 7.00–7.28 (m, 20 H, 4 × C_6H_5), 7.77, 8.13, 8.42, 8.74 (d, J = 7.8 Hz, 4 H, 4 × NH), 8.72 (br s, 2 H, NH_2) ppm; MS (+FAB) 662 ([M − TFA + 1]$^+$, M = $C_{42}H_{48}N_5O_6F_3$, TFA = $C_2HO_2F_3$); HRMS (+FAB) 662.3701 (calculated for [M − TFA + 1], $C_{40}H_{48}N_5O_4$ = 662.3706).

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaaza-3,6,9,12,15-pentamethylhexadecane (23a). To a solution of 1.0 M borane in tetrahydrofuran (30 mL) under N_2 was added (NMe)AlaAlaAlaAlaNHCH(CH_3)$_2$ (**22a**) (754 mg, 2.16 mmol) in THF (10 mL) dropwise and the temperature was kept at approximately 0 °C. The colorless solution was then heated to reflux for 36 h. The reaction mixture was cooled to room temperature, and 6 N aqueous HCl solution (10 mL) was added. After the tetrahydrofuran was removed under reduced pressure, NaOH pellets were added to saturate the aqueous phase and the product was extracted with chloroform (5 × 30 mL). The crude product was used for the next reaction: crude product yield 275 mg (57%).

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaaza-3,6,9,12-tetrabenzyl-15-methylhexadecane (23b). The reduction of (NMe)PhePhePhePheNHCH(CH_3)$_2$ (**22b**) (850 mg, 1.29 mmol) was carried out by the method described above to obtain the title compound. The crude product was not purified but used for the following reaction: crude product yield 453 mg (58%).

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaacetyl-2,5,8,11,14-pentaaza-3,6,9,12,15-pentamethylhexadecane (9b). Acetic anhydride (5 mL) was added dropwise to (3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-pentaaza-3,6,9,12,15-pentamethylhexadecane (**23a**) (137 mg, 0.45 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. After evaporation of excess acetic anhydride, the crude product was purified by column chromatography to give pure title compound: yield 207 mg (89%); R_f 0.25 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.05–1.47 (m, 18 H, $CH(CH_3)_2$ and 4 × CH_2CHCH_3), 1.98–2.32 (m, 15 H, 5 × $C(O)CH_3$), 2.79–4.80 (m, 16 H, CH_3N, $CH(CH_3)_2$, and 4 × CH_3CHCH_2) ppm; MS (+FAB) 512 ([M + 1]$^+$, M = $C_{26}H_{49}N_5O_5$).

Anal. Calcd for $C_{26}H_{49}N_5O_5$: C, 61.03; H, 9.65; N 13.69. Found: C, 60.97; H, 9.76; N, 13.54.

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaacetyl-2,5,8,11,14-pentaaza-3,6,9,12-tetrabenzyl-15-methylhexadecane (9d). Acetylation was conducted with (3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-pentaaza-3,6,9,12-tetrabenzyl-15-methylhexadecane (**23b**) (225 mg, 0.37 mmol) by the method described above, and the residue was purified by PTLC: yield 215 mg (70%); R_f 0.45 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 0.84–1.37 (m, 6 H, $CH(CH_3)_2$), 1.71–2.24 (m, 15 H, 5 × $C(O)CH_3$), 2.44–5.30 (m, 24 H, CH_3N, $CH(CH_3)_2$, and 4 × $CH(CH_2)_2$), 6.86–7.42 (m, 20 H, 4 × C_6H_5) ppm; MS (+FAB) 816 ([M + 1]$^+$, M = $C_{50}H_{65}N_5O_5$).

Anal. Calcd for $C_{50}H_{65}N_5O_5$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.54; H, 8.09; N, 8.81.

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaformyl-2,5,8,11,14-pentaaza-3,6,9,12,15-pentamethylhexadecane (9a). A mixture of acetic anhydride (2.5 mL) and formic acid (2.5 mL) was added dropwise to (3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-pentaaza-3,6,9,12,15-pentamethylhexadecane (**23a**) (137 mg, 0.45 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 8 h. After evaporation of the solvent, the crude material was purified by column chromatography to give the title compound: yield 154 mg (77%); R_f 0.18 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 1.08–1.56 (m, 18 H, $CH(CH_3)_2$ and 4 × CH_2-

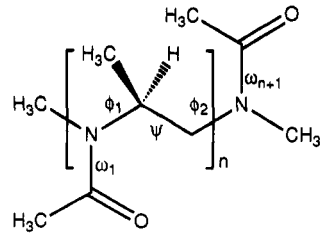


Figure 2. Schematic representation of poly(*N*-acetyl-1-methylethylenimine).

CHCH_3), 2.76–4.98 (m, 16 H, 5 × CH, 4 × CH_2 and CH_3N), 7.80–8.38 (m, 5 H, 5 × C(O)H) ppm; MS (+FAB) 442 ([M + 1]$^+$, M = $C_{21}H_{39}N_5O_5$).

Anal. Calcd for $C_{21}H_{39}N_5O_5$: C, 57.12; H, 8.90; N, 15.86. Found: C, 57.45; H, 8.98; N, 15.58.

(3*S*,6*S*,9*S*,12*S*)-2,5,8,11,14-Pentaformyl-2,5,8,11,14-pentaaza-3,6,9,12-tetrabenzyl-15-methylhexadecane (9c). The formylation of **23b** (225 mg, 0.37 mmol) was achieved by the method described above: yield 213 mg (77%); R_f 0.40 (10% methanol–chloroform); ^{1}H NMR ($CDCl_3$) δ 0.92–1.37 (m, 6 H, $CH(CH_3)_2$), 2.43–4.80 (m, 24 H, CH_3N, $CH(CH_3)_2$ and 4 × $CH(CH_2)_2$), 6.94–7.37 (m, 20 H, 4 × C_6H_5), 7.50–8.18 (m, 5 H, 5 × C(O)H) ppm; MS (+FAB) 746 ([M + 1]$^+$, M = $C_{45}H_{55}N_5O_5$).

Anal. Calcd for $C_{45}H_{55}N_5O_5$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.37; H, 7.53; N, 9.30.

Results and Discussion

It has been reported that poly[(*R*)-1-deuterio-*n*-hexyl isocyanate],[14] a macromolecule configurationally chiral only by virtue of deuterium substitution, exhibits a high optical rotation similar to what has been observed with optically active polycyanates containing the chiral center in the side chains.[15] These phenomena could be interpreted by the chiral perturbation in the pendant side chain group favoring one of the helical senses. Achiral poly(ethylenimine) in the anhydrous state obtained from poly(*N*-benzoylethylenimine) has been known to exist as double-stranded helices from X-ray structural analysis.[16] On the basis of these observations, optically active polyoxazolines having the chiral center in the backbone may be expected to assume stable helical structures. In order to examine the possibility of forming preferred helical arrays, molecular mechanics calculations were carried out for poly(*N*-acetyl-1-methylethylenimine) as well as for the monomer to tetramer model compounds ($CH_3[N(COCH_3)CH(CH_3)CH_2]_nN(COCH_3)CH_3$, n = 1–4) employing the flexible geometry Discover program.[11] A schematic structure of the molecular system is shown in Figure 2.

Conformational energy minimizations were first carried out for the monomer model compound (n = 1). Initial structures were generated in conformity with the rotational isomeric state approximation. With regard to rotations around CN–CC (ϕ), NC–CC (ψ), and CN–CO (ω) bonds, the following angles were assumed: ϕ = 0, 60, 120, 180, 240, and 300°, ψ = 60, 180, and 300°, ω = 0 and 180°. Six conformers were calculated as energy minima over a range of 2.5 kcal mol^{-1} above the global minimum value (Table I). Conformers with ψ around 60° are energetically less favored because of steric interactions: the N atom is located in the syn position to both $N(COCH_3)$ and side chain CH_3 groups of the preceding residue. For these six conformations, two different values of ω_2, i.e., 0 (cis) and 180° (trans), were calculated. The conformational energies of the structures with cis forms are shown in Table I because these structures are more stable for the polymer than structures with trans forms. As shown in Table I, on the other hand, the cis form was calculated for ω_1. Accordingly, the cis form was used for the further calculations.

Table I
Dihedral Angles ϕ_1, ψ, ϕ_2, and ω_1 Optimized for the Monomer Model (n = 1) and Relative Energies Calculated for the Monomer, Dimer (n = 2), and Tetramer (n = 4) Models

	dihedral angle per residue/deg				ΔE/kcal mol^{-1}		
conformer	ϕ_1	ψ	ϕ_2	ω_1	n = 1	n = 2	n = 4
I	66.1	65.2	−94.2	2.0	0.000		
II	74.4	69.6	72.7	2.2	0.441	0.442	1.909
III	66.0	164.7	95.8	1.5	0.794	1.642	4.550
IV	65.0	166.8	−75.7	0.9	1.266	2.087	5.524
V	−111.5	69.4	70.9	−1.2	1.297	0.000	4.090
VI	−113.9	165.2	−76.2	−0.3	2.065	1.709	0.000

Table II
Helical Parameters[a] Calculated for Poly(*N*-acetyl-1-methylethylenimine) (n = 20) Taking the Conformation III and VI Structures

conformer	helix	t/Å	d/Å	θ/deg	ΔE/kcal resd^{-1}
III	24/4 right-handed	25.2	1.10	62.6	1.246
VI	14/3 left-handed	17.8	1.27	−77.4	0.000

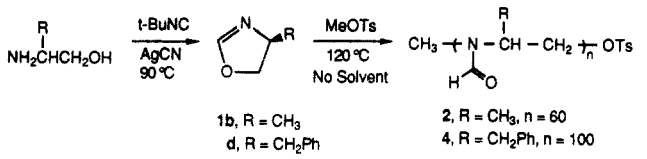
[a] The notions t, d, and θ represent the pitch of the helix, the rise along the helix axis per repeating unit, and the rotation angle about the helix axis per repeating unit, respectively.

Conformational energy calculations were carried out for the dimer (n = 2) and tetramer (n = 4) model compounds assuming that the continuing residues take the same conformation. The initial structures were generated by adopting the values of ϕ_1, ψ, and ω_2 estimated for the monomer model compound. The results of calculations are summarized in the last two columns of Table I. Conformer I which was the most stable in the case of the monomer model (n = 1) was prohibited for the dimer model compound by steric hindrance between the acetyl group of the first residue and the end terminal methyl group. Energy differences of the other five conformers II–VI are within ca. 2 kcal mol^{-1}. For the tetramer model compound (n = 4), conformer VI, which was least favored at the monomer level, was calculated to be the lowest energy arrangement.

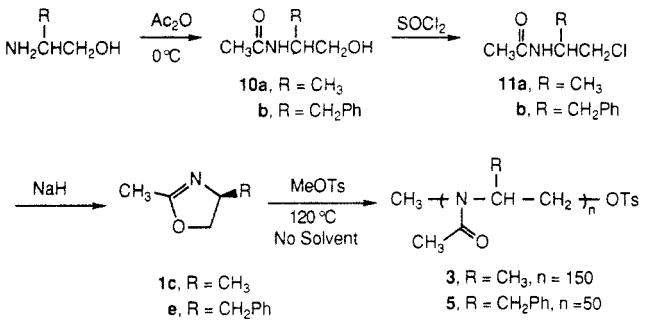
Similar studies were extended to the polymer with n = 20, assuming the conformers II–VI. Geometric parameters, optimized for the tetramer with the same conformations, were used for generating the initial structures. Stable helical arrays were calculated when the polymer assumed either conformer III or VI. Helical parameters and relative energies are given in Table II. The structure calculated for the polymer assuming conformer III is a right-handed helix containing 23 residues per four turns with the identity period of 25.2 Å. On the other hand, a left-handed helical structure of 14 residues per three turns with the identity period of 17.8 Å was estimated for the polymer assuming conformer VI. The latter left-handed helix is more stable than the conformer right-handed helix by 1.25 kcal/residue.

In order to investigate the conformations of optically active polymers experimentally, poly(*N*-formyl-1-methylethylenimine) (**2**), poly(*N*-acetyl-1-methylethylenimine) (**3**), poly(*N*-formyl-1-benzylethylenimine) (**4**), and poly(*N*-acetyl-1-benzylethylenimine) (**5**) were synthesized. There are many methods known for the preparation of 2-oxazolines.[17] One method is based on the dehydration of *N*-(hydroxyalkyl)carboxamide. The dehydration is normally achieved in the gas phase with a solid-acid catalyst. Effective dehydrating agents used are alumina, sulfuric acid, and thionyl chloride. Another method involves the dehalogenation of a haloamide. A strong base such as sodium hydroxide is often used as a dehalogenating agent. Oxazolines can also be obtained by the isomerization of *N*-acylaziridines. The *N*-acylaziridines give

Scheme I
Preparation of *N*-Formyl Polymers



Scheme II
Preparation of *N*-Acetyl Polymers

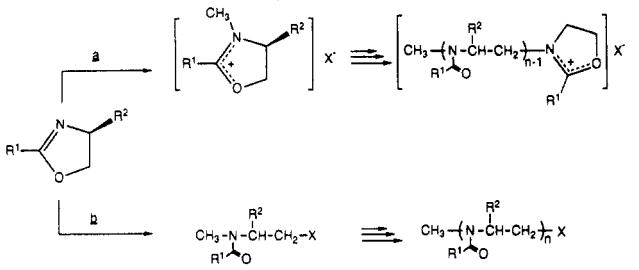


2-substituted 2-oxazolines where the isomerization is achieved by heat or acidic, tertiary amine, or nucleophilic ion catalysts. Cyclization of hydroxyalkyl isocyanide yields 2-oxazolines. The intramolecular addition of a hydroxyl group to the isocyanide carbon in hydroxyalkyl isocyanide gives 2-unsubstituted 2-oxazoline. This reaction is catalyzed by copper(I) oxide as well as by salts of transition metals such as palladium, platinum, and gold. Still another method involves a reaction of nitriles with amino alcohols. Aromatic as well as aliphatic nitriles react with amino alcohols to produce 2-substituted 2-oxazolines. The last reported method is the cyclization of amino alcohols with isocyanide. The reaction of amino alcohols with *tert*-butyl isocyanide in the presence of a transition-metal catalyst produces 2-unsubstituted 2-oxazolines. We employed the isocyanide method for the preparation of 2-oxazolines (**1b** and **1d** in which R^1 = H in both molecules) since the reaction conditions were milder than other methods and we could avoid any possible racemization.

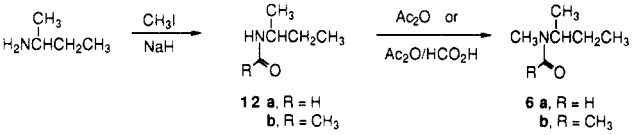
The monomeric 4-methyl-2-oxazoline (**1b**) and 4-benzyl-2-oxazoline (**1d**), starting materials for the *N*-formyl polymers (i.e., **2** and **4**), were prepared by Saegusa's method[3] from L-alaninol and L-phenylalaninol using *tert*-butyl isocyanide in the presence of silver cyanide (Scheme I). In the purification step, codistillation of the product with impurities was an existing problem. However, we removed byproduct(s) and unreacted starting materials effectively by treatment with ion-exchange resin (Amberlite IRC-50) followed by distillation under reduced pressure. On the other hand, 2,4-dimethyl-2-oxazoline (**1c**) and 4-benzyl-2-methyl-2-oxazoline (**1e**), for the *N*-acetyl polymers (i.e., **3** and **5**), were prepared by the Muchowski's method[18] as depicted in Scheme II. Here, 1-methyl-2-pyrrolidinone, used as a solvent for the cyclization step, could be completely removed by repeated distillations under reduced pressure.

Polymerizations of monomeric 2-oxazolines (**1b–e**) were carried out in sealed tubes at 120 °C for 10–72 h using methyl *p*-toluenesulfonate as an initiator. The polymerization process is very sensitive to moisture and any other impurities. The glassware must be dried more than 24 h in an oven. All the reagents must be distilled before use and transferred by cannulas. We examined other initiators (methyl iodide, dimethyl sulfate) and reaction temperatures (70–120 °C) in the absence and presence of solvent (acetonitrile, *N*,*N*-dimethylformamide, toluene).

Scheme III
Two Different Polymerization Mechanisms



Scheme IV
Preparation of Monomeric Model Compounds 6a–b



The best results were obtained when the above conditions were employed which were the same as Saegusa's methods.[19] Polymerizations of 2-oxazolines were known to proceed via two different mechanisms depending on the nature of 2-oxazolines and initiators (Scheme III).[20] One mechanism proceeds with a cationic oxazolinium ring propagation species (path a), and the other proceeds with a covalent propagation species (path b). According to the Saegusa's observations, since the tosylate anion is less nucleophilic than 2-oxazolines (**1b–e**), our polymerization would have proceeded through the cationic oxazolinium propagation species. As the polymerization progressed, the polymer layer, as a glasslike semisolid, grew from the bottom of the sealed tube. After the polymerization was complete, a small amount of methanol was added to the reaction mixture and the polymer precipitated as a white solid upon the addition of ether. The average degree of polymerization of these polymers (**2–5**) was between 50 and 150 based on the NMR integrations and intrinsic viscosity measurements. Molecular weights of the polymers were proportional to the monomer:initiator ratios as shown in Schemes I and II.

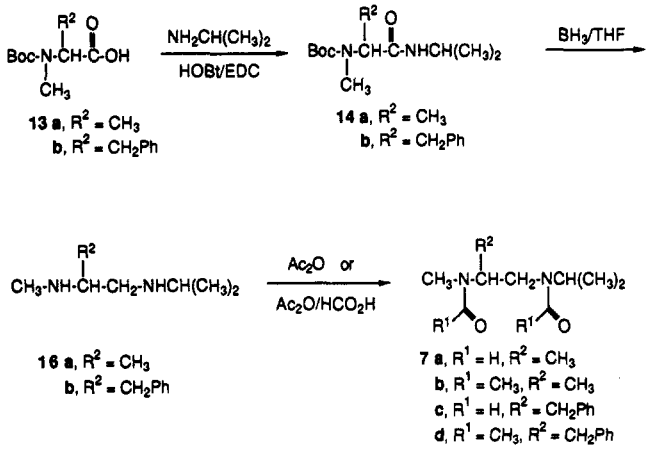
For the conformational analysis of these polymers, mainly for the comparison of the CD and NMR measurements, we synthesized four different types of model compounds. The first class of model compounds (**6a–b**) has one chiral center and one amide group. The second (**7a–d**), third (**8a–d**), and fourth (**9a–d**) type model compounds have one, two, and four chiral centers and two, three, and five amide groups, respectively.

Compounds **6a,b** were synthesized from the optically pure (*S*)-2-butylamine by acylation and methylation (Scheme IV). A cis–trans isomerism was observed for both compounds arising from the side-chain amide group. We defined the geometric forms of cis and trans according to the Cahn–Ingold–Prelog convention. The cis:trans ratio observed for **6a** was 4:1 in hexafluoro-2-propanol-d_2 and 2:1 for **6b** in the same solvent (Table III). The second, third, and fourth classes of model compounds were prepared by similar pathways and depicted in Schemes V–VII, respectively. A typical procedure can be described by the synthesis of the fourth type of model compounds (Scheme VII). To prepare the compounds **9a–d**, BocAlaOH or BocPheOH was treated with methyl iodide in the presence of sodium hydride to give Boc(NMe)AlaOH or Boc(NMe)PheOH. After coupling of BocAlaOH with 2-propylamine using 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC), the *tert*-butyloxycarbonyl (Boc) group

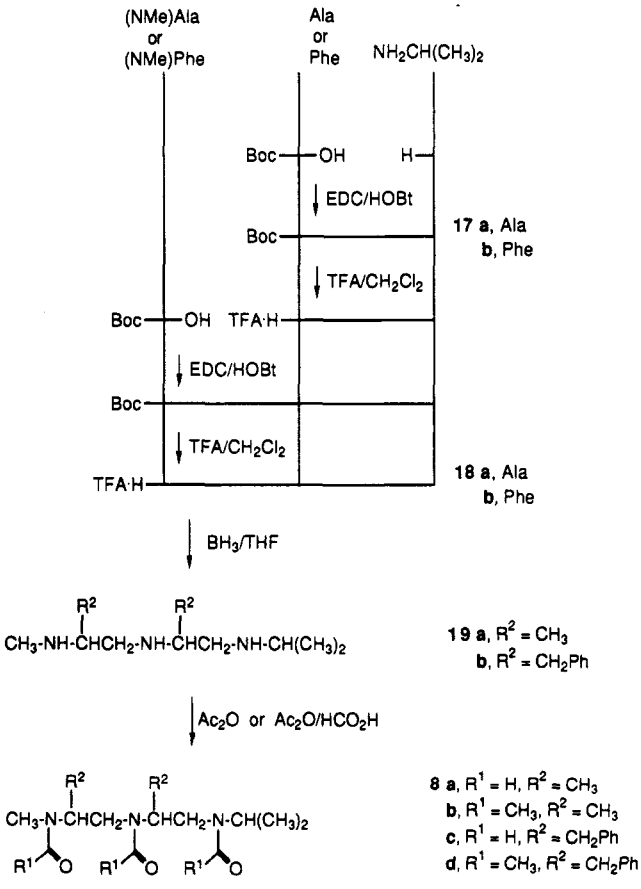
Table III
Cis:Trans Ratios Observed for Compounds 6a and 6b in Hexafluoro-2-propanol and Chloroform

solvent	compd 6a	compd 6b
HF-2-P	80:20	64:36
$CDCl_3$	80:20	50:50

Scheme V
Preparation of Monomeric Model Compounds 7a–d

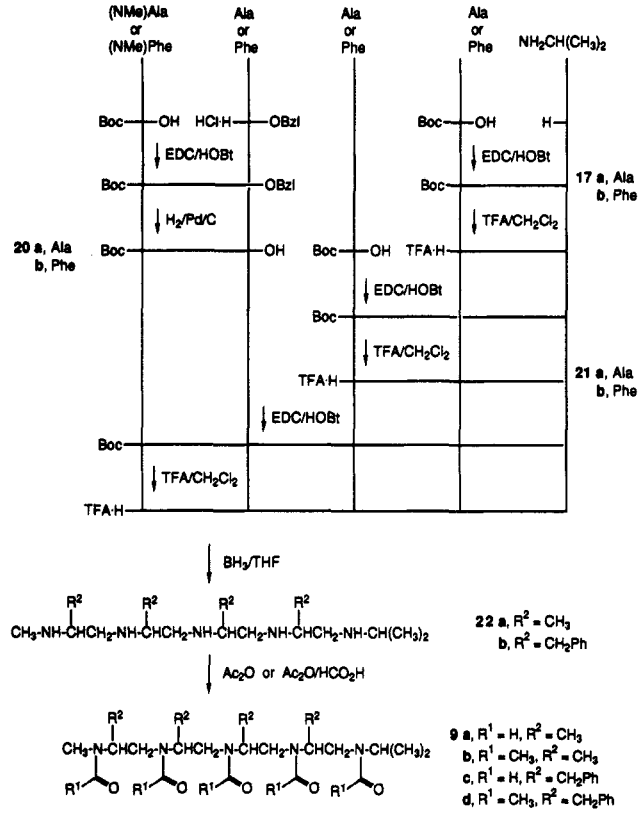


Scheme VI
Preparation of Dimeric Model Compounds 8a–d

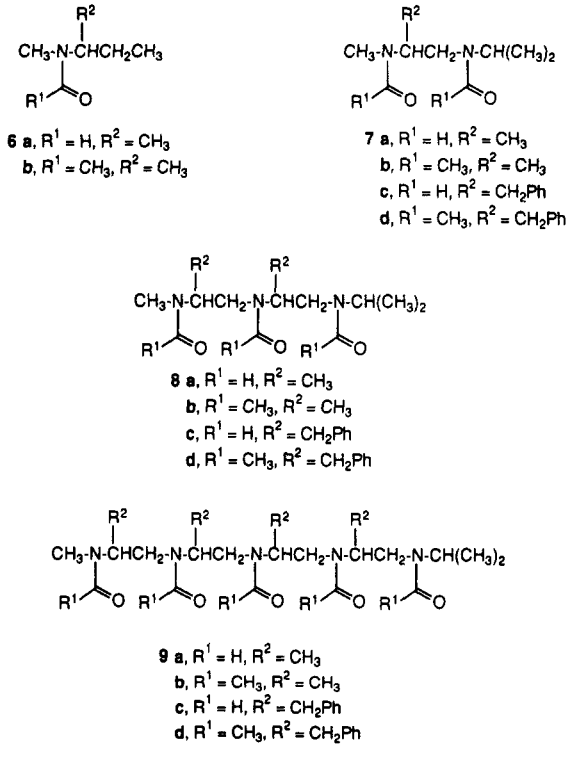


was removed with trifluoroacetic acid. The resulting AlaNHCH$(CH_3)_2$ was successively coupled with BocAlaOH, BocAlaOH, and Boc(NMe)AlaOH to give Boc(NMe)-AlaAlaAlaAlaNHCH$(CH_3)_2$. After reduction with borane to give pentaamine, acylation furnished the desired model

Scheme VII
Preparation of Tetrameric Model Compounds 9a–d

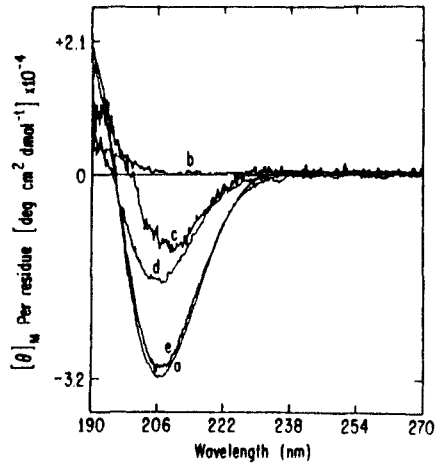


compounds **9a–d**. These second, third, and fourth classes of model compounds (**7a–d, 8a–d, 9a–d**) showed complicated NMR patterns because of cis–trans isomerism of the amide groups.



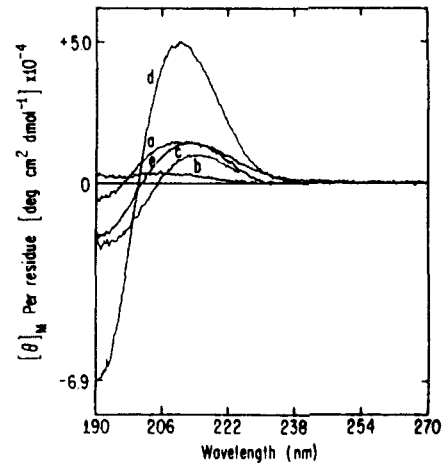
Turning to the CD spectra, Figure 3 shows the spectra of the polymers and their model compounds at 20 °C. The intensities of model compounds were normalized for the number of chiral centers in each molecule. Several interesting patterns were observed for these compounds. The alanine polymers and their model compounds have

(i) Formyl-Ala derivatives



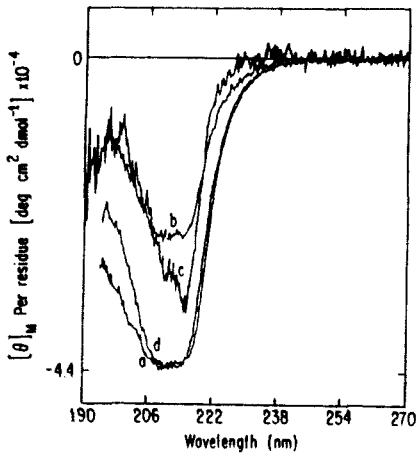
a) Polymer 2
b) Model compound **6a**
c) Model compound **7a**
d) Model compound **8a**
e) Model compound **9a**

(ii) Acetyl-Ala derivatives



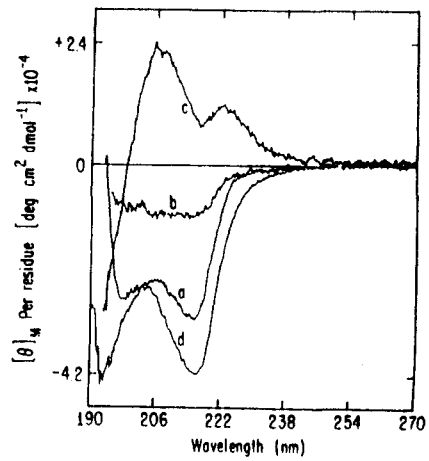
a) Polymer **3**
b) Model compound **6b**
c) Model compound **7b**
d) Model compound **8b**
e) Model compound **9b**

(iii) Formyl-Phe derivatives



a) Polymer **4**
b) Model compound **7c**
c) Model compound **8c**
d) Model compound **9c**

(iv) Acetyl-Phe derivatives



a) Polymer **5**
b) Model compound **7d**
c) Model compound **8d**
d) Model compound **9d**

Figure 3. Circular Dichroism (CD) spectra of polymers and model compounds.

only one chromophore (the amide group) and give a broad CD absorption. On the other hand, phenylalanine derivatives have two chromophores (the amide and the phenyl groups) and give at least two CD bands. The acetyl derivatives of the model compounds show positive Cotton effects while formyl derivatives give negative Cotton effects. These patterns are likely attributed to the geometric conformational arrays of the model compounds. In most of the cases the intensity increases with the increasing number of chromophores. We were able to show that the polymers do not aggregate by measuring both the polymers and model compounds at a concentration of 0.02, 0.1, and 0.5 mg/mL in hexafluoro-2-propanol. The CD spectra of all compounds were the same at all concentrations over this range. Lastly and most importantly, the CD spectra of polymers and tetrameric model compounds gave the same shapes and same intensities. This observation strongly supports our initial findings that polymers and tetrameric model compounds have the same conformations as established from our molecular mechanics calculations.[9] Conformational studies of the polymers and model compounds using NMR spectroscopy will provide important information about the preferred conformations around the N–CHR_2, C–C, and CH_2–N bonds in the backbone. Energy differences between the rotational isomeric states around these bonds could be estimated from the vicinal ^1H–^1H and ^{13}C–^1H coupling constants.

Conclusions

The polymerization of optically active 2-oxazolines is very sensitive to impurities. We have obtained 2-oxazolines in pure form using ion-exchange resins. These routes were especially useful for low-boiling 2-oxazolines such as 4-methyl-2-oxazoline and 2,4-dimethyl-2-oxazoline. From the CD spectra we have confirmed that the tetrameric

model compounds and corresponding polymers have similar chromophoric arrays and thus likely have similar conformations. After completion of our NMR studies, we hope to relate experimentally derived structures to those calculated by flexible geometry energy calculations. Following these efforts we will begin to study these polymers as novel biomaterials.

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Registry No. **1b**, 53744-57-3; **1c**, 131830-49-4; **1d**, 75866-71-6; **1e**, 75866-72-7; **2** (homopolymer), 58578-53-3; **2** (SRU), 53745-65-6; **3** (homopolymer), 143731-76-4; **3** (SRU), 143509-95-9; **4** (homopolymer), 143509-91-5; **4** (SRU), 143509-94-8; **5** (homopolymer), 143509-92-6; **5** (SRU), 143509-93-7; **6a**, 143546-56-9; **6b**, 143546-55-8; **7a**, 143546-60-5; **7b**, 143546-59-2; **7c**, 143546-62-7; **7d**, 143546-61-6; **8a**, 143546-70-7; **8b**, 143546-68-3; **8c**, 143546-71-8; **8d**, 143546-69-4; **9a**, 143546-83-2; **9b**, 143546-81-0; **9c**, 143546-84-3; **9d**, 143546-82-1; **10a**, 35593-62-5; **10b**, 52485-51-5; **11a**, 143546-53-6; **11b**, 143546-54-7; **12a**, 61852-43-5; **12b**, 64528-61-6; **13a**, 16948-16-6; **13b**, 37553-65-4; **14a**, 77975-71-4; **14b**, 143564-46-9; **16a**, 143546-57-0; **16b**, 143546-58-1; **17a**, 84851-02-5; **17b**, 143546-63-8; **18a**, 143546-64-9; **18b**, 143546-65-0; **19a**, 143546-66-1; **19b**, 143546-67-2; **20a**, 143546-72-9; **20b**, 143546-73-0; **21a**, 143546-75-2; **21b**, 143546-76-3; **22a**, 143546-78-5; **22b**, 143546-80-9; **23a**, 143564-47-0; **23b**, 143564-48-1; (*S*)-2-amino-1-propanol, 2749-11-3; *tert*-butyl isocyanide, 7188-38-7; acetic anhydride, 108-24-7; (*S*)-2-butylamine, 513-49-5; 2-propylamine, 75-31-0; (*S*)-2-amino-3-phenyl-1-propanol, 3182-95-4.