Synthesis and Characterization of Chiral N−O Turns Induced by α-Aminoxy Acids

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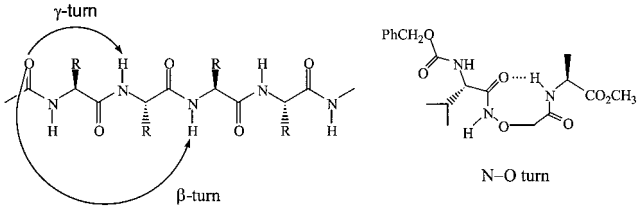
Chiral α-aminoxy acids of various side chains were synthesized with high optical purity starting from chiral α-amino acids. The conformations of diamides **13a**−**e**, **15**, and **16** were probed by using NMR, FT-IR, and CD spectroscopic methods as well as X-ray crystallography. The right-handed turns with eight-membered-ring intramolecular hydrogen bonds between adjacent residues (called the N−O turns) were found to be preferred for D-aminoxy acid residues, and they were independent of the side chains. The rigid chiral N−O turns should have great potential in molecular design.

Introduction

In biological systems, turn structures play critical roles in the recognition of receptors, enzymes, and antibodies.[1] As β-turns are one of the three major classes of peptide and protein secondary structures, significant effort has been made to design and synthesize β-turn mimetics for elucidation of molecular recognition and drug discovery.[2−11] In contrast, γ-turns, which involve a seven-membered-ring hydrogen bond, are much less common in proteins and peptides.[12−15]



Due to the repulsion of lone-pair electrons of nitrogen and oxygen atoms, α-aminoxy acids should have rigid conformations[16] and modulate the hydrogen bond donor and acceptor properties of adjacent amide groups. We previously reported that α-aminoxyacetic acid induced a strong eight-membered-ring hydrogen bond between adjacent amino acid residues (the N−O turn),[17] which can be considered as an extended γ-turn.[18,19]

For peptides of α-amino acids, the propensity of turn formation depends on the nature, position, and relative configuration of amino acid residues. Therefore, it is

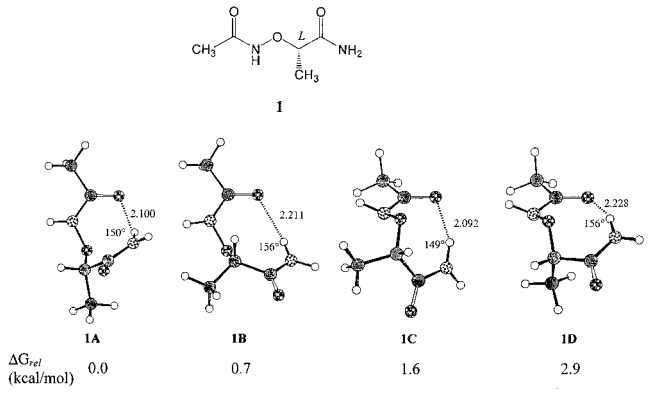


Figure 1. HF/6-31G**-optimized structures of compound **1** (only the four lowest-energy conformations are shown).

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(1) (a) Creighton, T. E. *Proteins: Structures and Molecular Principles*, 2nd ed.; Freeman: New York, 1993. (b) Rose, G. D.; Gierash, L. m.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1−109.
(2) Kahn, M. *Synlett* **1993**, 821−826.
(3) Bach, A. C., II; Espina, J. R.; Jackson, S. A.; Stouten, P. F. W.; Duke, J. L.; Mousa, S. A.; DeGrado, W. F. *J. Am. Chem. Soc.* **1996**, *118*, 293−294.
(4) Eguchi, M.; Lee, M. S.; Nakanishi, H.; Stasiak, M.; Lovell, S.; Kahn, M. *J. Am. Chem. Soc.* **1999**, *121*, 12204−12205.
(5) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806−1816.
(6) Gallo, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 9774−9788.
(7) Virgilio, A. A.; Bray, A. A.; Zhang, W.; Trinh, L.; Snyder, M.; Morrissey, M. M.; Ellman, J. A. *Tetrahedron* **1997**, *53*, 6635−6644.
(8) Souers, A. J.; Virgilio, A. A.; Rosenquist, Å.; Fenuik, W.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 1817−1825.
(9) Feng, Y.-B.; Wang, Z.-C.; Jin, S.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 10768−10769.
(10) Feng, Y.-B.; Pattarawarapan, M.; Wang, Z.-C.; Burgess, K. *J. Org. Chem.* **1999**, *64*, 9175−9177.
(11) Müller, G.; Hessler, G.; Decornez, H. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 894−896.
(12) Khaled, M. A.; Urry, D. W.; Okamoto, K. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 162−169.
(13) Pavone, V.; Lombardi, A.; D'Auria, G.; Saviano, M.; Nastri, F.; Paolillo, L.; Di Blasio, B.; Pedone, C. *Biopolymers* **1992**, *32*, 173−183.
(14) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1994**, *116*, 799−800.
(15) Jiménez, A. I.; Cativiela, C.; Marraud, M. *Tetrahedron Lett.* **2000**, *41*, 5353−5356.
(16) (a) Riddell, F. G. *Tetrahedron* **1981**, *37*, 849. (b) Raban, M.; Kost, D. *Tetrahedron* **1984**, *40*, 3345. (c) For an insightful discussion of the conformational preference of the N−O bond in relation to calicheamicin−DNA interactions, see: Walker, S.; Gange, D.; Gupta, V.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 3197−3206.
(17) Yang, D.; Ng, F.-F.; Li, Z.-J.; Wu, Y.-D.; Chan, K. W.-K.; Wang, D.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9794−9795.
(18) A similar extended γ-turn reported by Marraud involves an eight-membered-ring hydrogen bond between an amide carbonyl group and the hydroxyl group of N-hydroxy amides: Dupont, V.; Lecoq, A.; Mangeot, J.-P.; Aubry, A.; Boussard, G.; Marraud, M. *J. Am. Chem. Soc.* **1993**, *115*, 8898−8906.
(19) Thévenet, L.; Vanderesse, R.; Marraud, M.; Didierjean, C.; Aubry, A. *Tetrahedron Lett.* **2000**, *41*, 2361−2364.

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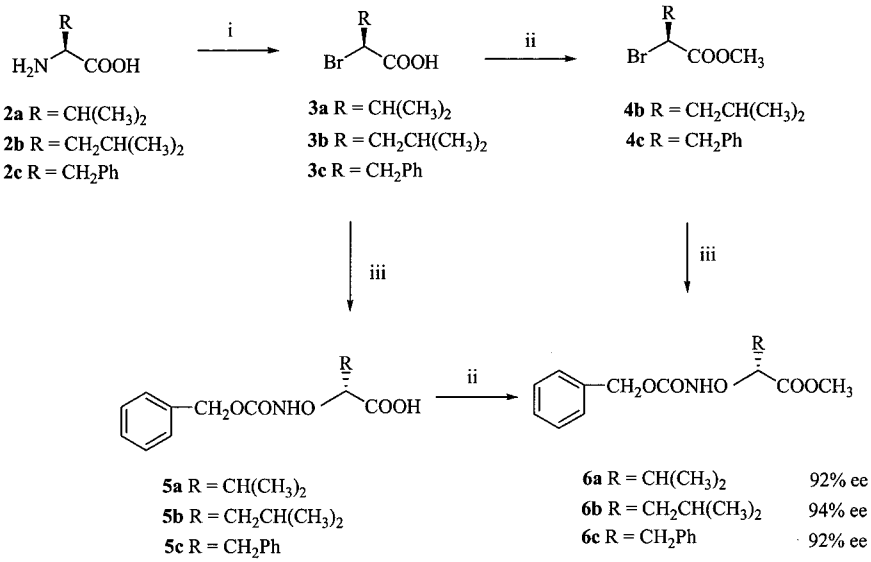
Scheme 1[a]



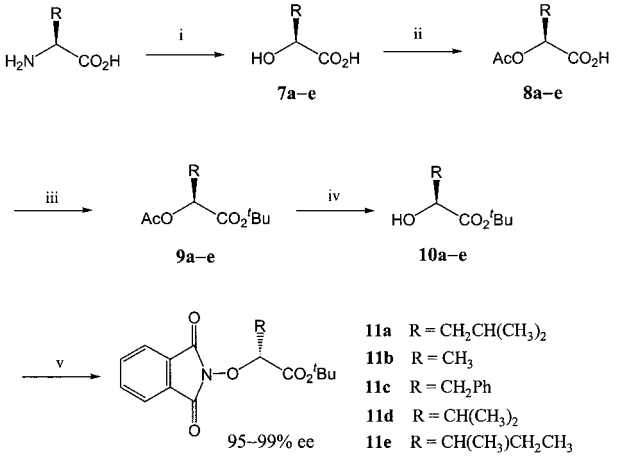
[a] (i) $NaNO_2$, KBr, H_2SO_4 at 0−5 °C; (ii) CH_3OH, $SOCl_2$, rt; (iii) CbzNHOH, NaH, DMF at 0−5 °C.

interesting to probe whether or not the eight-membered-ring hydrogen-bonded N−O turns are still favored when side chains are introduced to α-aminoxyacetic acid. According to the ab initio molecular orbital calculations,[19] the four lowest-energy conformers (**1A**−**D**) of L-α-aminoxypropionic acid diamide **1** were found to contain eight-membered-ring hydrogen bonds (Figure 1). The $\angle NOC_\alpha C_O$ angles were negative for **1A** and **1B** but positive for **1C** and **1D**. Thus, the hydrogen bonding pattern of **1A** or **1B** allowed a left-handed turn, while that of **1C** or **1D** resulted in a right-handed turn. The ab initio calculation results suggested that chiral α-aminoxy acids of L-configuration should prefer a left-handed chiral N−O turn (**1A** or **1B**). Furthermore, the α-methyl group was anti to the N−O bond in **1A** but gauche in **1B**, which made **1A** the most stable conformation. In this paper, we report our experimental work on the synthesis and characterization of chiral N−O turns induced by α-aminoxy acids.[21]

Results and Discussion

Synthesis of Chiral α-Aminoxy Acids. Testa[22] reported a method for synthesizing chiral α-aminoxy acids, but the optical purities of the α-aminoxy acids were not reported in the literature.[23] We used this method to synthesize several D-α-aminoxy acids from natural L-α-amino acids (**2a**−**c**) with overall yields of α-aminoxy esters **6a**−**c** in the range of 36−55% (Scheme 1). While the conversion of L-α-amino acids to α-bromo acids proceeded with high retention at the α-carbon, nucleophilic displacement of α-bromo acids with CbzNHOH followed an S_N2 mechanism with inversion of configuration to afford D-α-aminoxy acids. The optical purities of α-aminoxy esters **6a**−**c** were found to be in the range of 92−94% as determined by HPLC analysis.

Scheme 2[a]



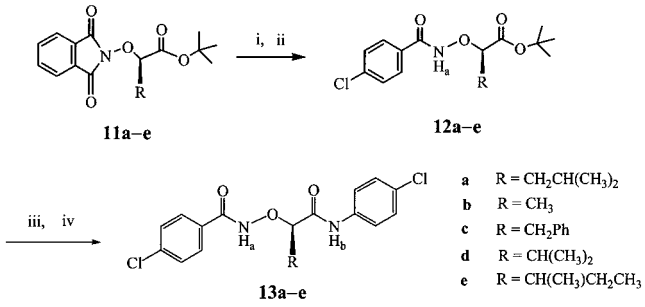
[a] (i) $NaNO_2$, H_2SO_4, H_2O, 80−95%; (ii) AcCl, reflux, 95%; (iii) DCC, *t*-BuOH, DMAP, CH_2Cl_2, 75−90%; (iv) K_2CO_3, MeOH, H_2O, 85−98%; (v) *N*-hydroxyphthalimide, DEAD, PPh_3, THF, 69−83%.

The Cbz protecting group of α-aminoxy acids was difficult to remove under mild conditions. For example, the hydrogenation method cannot be used because the free α-aminoxy acids obtained can be further hydrogenated to give α-hydroxy acids.[23]

We developed a general method for the synthesis of chiral α-aminoxy acids as shown in Scheme 2. The diazotization of L-α-amino acids gave α-hydroxy acids **7a**−**e** with retention of configuration at the α-carbon due to the neighboring-group participation.[24] Acetylation, DCC coupling, and deacetylation yielded **10a**−**e** with retention of configuration. The Mitsunobu reaction[25] of the *tert*-butyl esters **10a**−**e** afforded the protected α-aminoxy acids **11a**−**e** with inversion of configuration at the α-carbon. The overall yields for syntheses of α-aminoxy

(20) Wu, Y.-D.; Wang, D.-P.; Chan, K. W. K.; Yang, D. *J. Am. Chem. Soc.* **1999**, *121*, 11189−11196.
(21) For preliminary results, see: Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589−590.
(22) Testa, E.; Nicolaus, B. J. R.; Mariani, L.; Pagani, G. *Helv. Chim. Acta* **1963**, *46*, 766.
(23) Briggs, M. T.; Morley, J. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2138−2143.
(24) Brewster, P.; Hiron, F.; Hugers, E. D.; Ingold, C. K,; Rao, P. A. D. S. *Nature* **1950**, *166*, 179−180.
(25) Mitsunobu, O. *Synthesis* **1981**, 1−28.

Scheme 3[a]



[a] (i) $NH_2NH_2 \cdot H_2O$, MeOH; (ii) 4-chlorobenzoic acid, EDCI, HOBt, CH_2Cl_2, 61−95%; (iii) TFA, CH_2Cl_2; (iv) 4-chloroaniline, EDCI, HOBt, CH_2Cl_2, 65−84%.

acids were in the range of 36−56%, and no purification was needed for most of the steps. The optical purities of chiral α-aminoxy acids **11a**, **11c**, and **11d** were found to be 95−99% by HPLC analysis, which indicates that very little or no racemization occurred in the synthesis of chiral α-aminoxy acids. Furthermore, the phthaloyl group can be cleaved with hydrazine hydrate, whereas the *tert*-butyl group can be easily removed with trifluoroacetic acid. The orthogonal conditions for deprotection of phthaloyl and *tert*-butyl groups make α-aminoxy acids **11a**−**e** ideal building blocks for peptide synthesis.[26]

Design and Synthesis of α-Aminoxy Diamides for Circular Dichroism Exciton Coupling Study. The circular dichroism (CD) exciton coupling method[27] was used to determine the handedness of the chiral N−O turns. Compounds **13a**−**e** were designed with two *p*-chlorophenyl chromophores of similar $\pi \rightarrow \pi^*$ absorptions at both termini. They were expected to exhibit a strong Cotton effect due to the exciton coupling. Compounds **13a**−**e** were synthesized starting from bisprotected D-α-aminoxy acids **11a**−**e** (Scheme 3). Deprotection of the phthaloyl group using hydrazine hydrate in methanol gave the free aminoxy group, which was then coupled with 4-chlorobenzoic acid using standard peptide coupling methods to provide compounds **12a**−**e**. Treatment of compounds **12a**−**e** with trifluoroacetic acid in CH_2Cl_2 followed by coupling with 4-chloroaniline using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methyliodide (EDCI)/1-hydroxybenzotriazole (HOBt) afforded the D-α-aminoxy diamides **13a**−**e**.

Diamides **15** and **16** containing only one *p*-chlorophenyl chromophore were also designed and synthesized (Scheme 4). In contrast to **13a**−**e**, these monochromophoric compounds should give a weak Cotton effect as no exciton coupling would occur.

^{1}H NMR Studies of Chiral D-α-Aminoxy Diamides 13a−e, 15, and 16.[6,21,28] ^{1}H NMR dilution studies of diamides **13a**−**e**, **15**, and **16** (Figure 2) showed that the chemical shifts of NH_b's changed very little upon dilution with CD_2Cl_2, whereas the chemical shifts of NH_a's apparently moved upfield.

Table 1. UV and CD Data of Compounds 13a, 15, and 16 in MeOH

	13a	15	16
UV	246 nm (ϵ = 10 466)	250 nm (ϵ = 6433)	240 nm (ϵ = 6067)
CD	261 nm ($\Delta\epsilon$ = +10.1) 235 nm ($\Delta\epsilon$ = −4.5)	251 nm ($\Delta\epsilon$ = +2.6) 224 nm ($\Delta\epsilon$ = −1.6)	no strong Cotton effect above 230 nm was found

DMSO-d_6 titration studies of **13a**−**e**, **15**, and **16** (2 mM in $CDCl_3$) (Figure 3) showed that the chemical shift of H_a at the N-terminus had a dramatic downfield shift, whereas H_b at the C-terminus showed little change upon addition of DMSO-d_6.

These ^{1}H NMR studies suggest that the N-terminus protons (H_a's) of diamides **13a**−**e**, **15**, and **16** are solvent accessible, whereas C-terminus ones (H_b's) are intramolecularly hydrogen bonded. That is, the N−O turn is maintained when a side chain is introduced to α-aminoxyacetic acids.

FT-IR Studies of Chiral D-α-Aminoxy Diamides 13a, 15, and 16.[29] FT-IR spectra of the N−H stretch region of compounds **13a**, **15**, and **16** at a 1 mM concentration in CH_2Cl_2 are shown in Figure 4. For compound **13a**, the peak at 3345 cm^{-1} corresponded to the non-hydrogen-bonded amide N−H at the N-terminus. The peaks in the region of 3300−3100 cm^{-1} were assigned to the stretching bands of the hydrogen-bonded amide N−H at the C-terminus, and the multiplicity was probably due to the vibrational coupling of the C-terminal amide N−H with its adjacent aryl group. For compound **15**, the peak at 3379 cm^{-1} corresponded to the non-hydrogen-bonded N-terminal amide N−H, whereas absorptions in the region of 3300−3100 cm^{-1} were assigned to an intramolecular hydrogen-bonded amide N−H at the C-terminus, the pattern of which was complicated again by the vibrational coupling of the C-terminal amide N−H with its adjacent aryl group. The spectrum of compound **16** showed a broad peak at 3341 cm^{-1}, assigned as the stretching band of the hydrogen-bonded *N*-isobutyl amide N−H overlapped with that of the non-hydrogen-bonded *N*-oxy amide N−H. The small peak at 3433 cm^{-1} corresponded to the non-hydrogen-bonded isobutyl amide N−H.

The FT-IR studies revealed that the α-aminoxy diamides **13a**, **15**, and **16** adopted predominantly the intramolecular eight-membered-ring hydrogen-bonded conformations.

CD Studies for Diamides 13a−e, 15, and 16.[27] The UV and CD data of compounds **13a**, **15**, and **16** in MeOH are shown in Table 1. Due to the presence of two chromophores, the UV spectrum of compound **13a** exhibited the charge-transfer transition band at λ_{max} = 246 nm, and its molar extinction coefficient (ϵ = 10 466) was almost twice of that for compound **15** or **16**.

The CD spectrum of compound **15** revealed a relatively weak positive Cotton effect ($\Delta\epsilon$ = +2.6) in the region of the electronic charge-transfer band at λ_{max} = 251 nm, while no strong Cotton effect above 230 nm was found for compound **16** (Figure 5a). In contrast, the CD spectrum of compound **13a** showed two very strong Cotton effects of opposite signs: the first Cotton effect at the longer wavelength (261 nm) had a value of $\Delta\epsilon$ = +10.1,

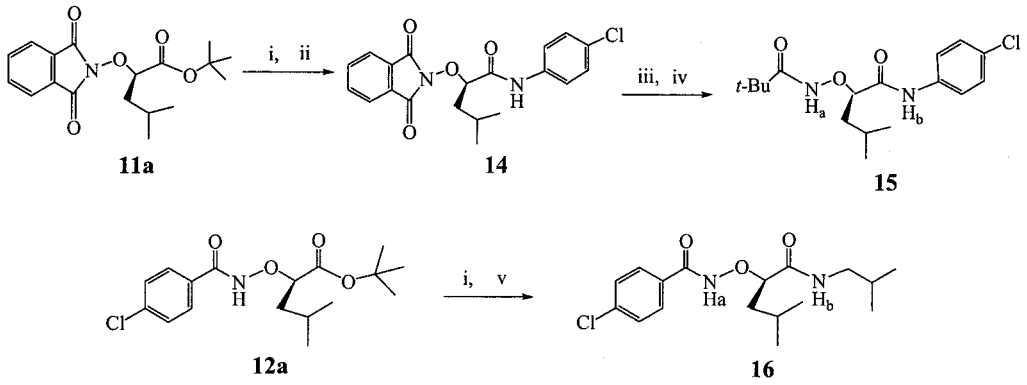
(26) While the manuscript was in preparation, Shin et al. reported the synthesis of chiral phthaloyl D-α-aminoxy acid monomers with benzyl ester as the C-terminal protecting group. See: Shin, I.; Lee, M.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667−7675.

(27) Harada, N.; Nakanishi, K. In *Circular Dichroic Spectroscopy*: *Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(28) Gellman, S. H.; Dado, G. P.; Liang, G. B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164−1173.

(29) For a review of IR studies of intramolecular hydrogen bonds in small molecules, see: Aaron, H. S. *Top. Stereochem.* **1980**, *11*, 1.

Scheme 4[a]



[a] (i) TFA, CH_2Cl_2; (ii) 4-chloroaniline, EDCI, HOBt, CH_2Cl_2, 80%; (iii) $NH_2NH_2 \cdot H_2O$, MeOH; (iv) pivaloyl chloride, $NaHCO_3$, CH_2Cl_2, H_2O, 93%; (v) isobutylamine, EDCI, HOBt, CH_2Cl_2, 78%.

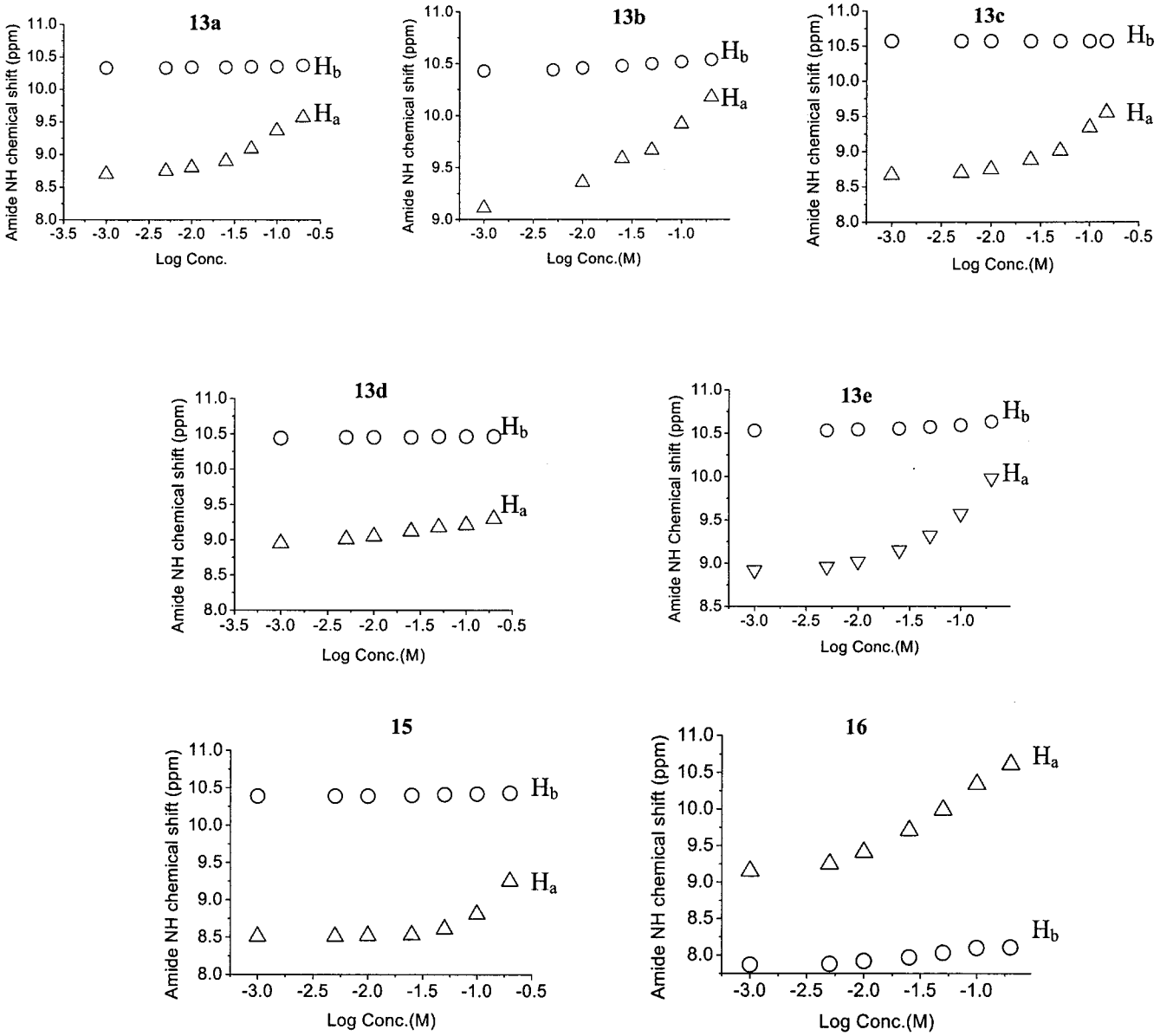


Figure 2. ^1H NMR chemical shifts of amide protons of **13a**−**e**, **15**, and **16** in CD_2Cl_2 at 25 °C as a function of the logarithm of concentration.

while the second Cotton effect at the shorter wavelength (235 nm) had a value of $\Delta\epsilon = -4.5$. Thus, a positive exciton coupling was observed for compound **13a**.

For compound **13a**, the chirality between the long axes of the two chromophores is approximated by that between the N−O bond and the $C_\alpha-C_O$ bond due to the favorable

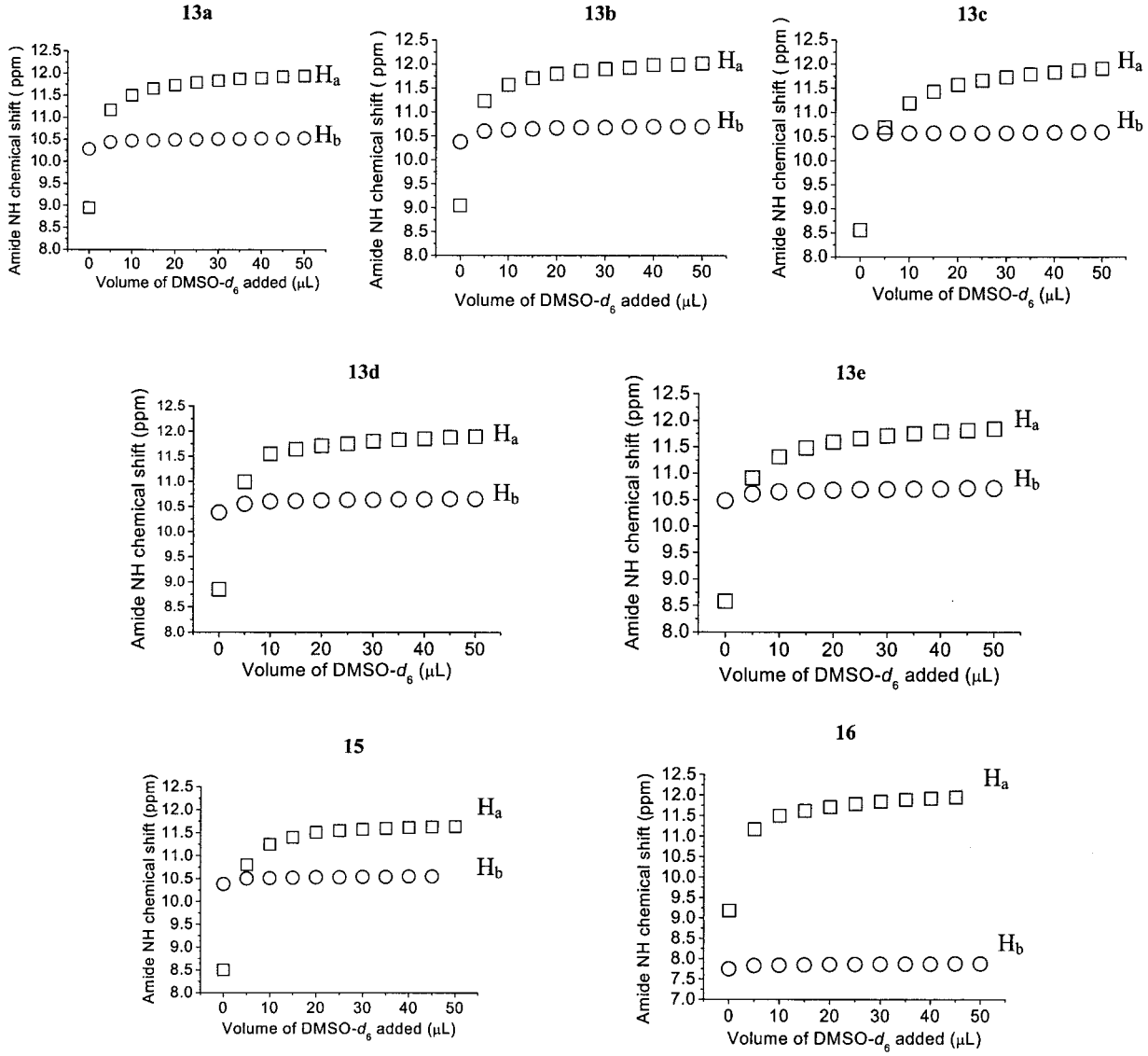


Figure 3. ^{1}H NMR chemical shifts of amide protons of **13a**−**e**, **15**, and **16** (2 mM in 0.5 mL of $CDCl_3$) at 25 °C when increasing amounts of DMSO-d_6 were added.

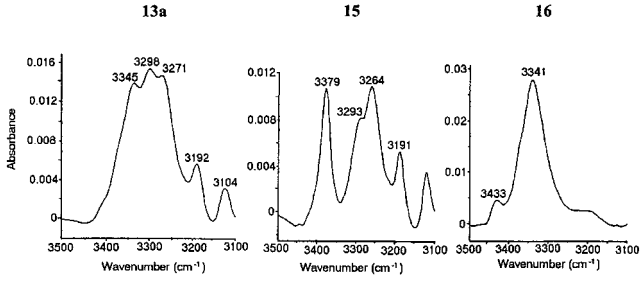


Figure 4. N−H stretch region of FT-IR spectra for compounds **13a**, **15**, and **16** at 1 mM in CH_2Cl_2 at room temperature.

planar *s*-trans conformation of amide bonds (Figure 5b). In other words, the absolute chirality of the N−O and C_α−C_O bonds, which is the dihedral angle ∠$NOC_\alpha C_O$, can be determined by the signs of Cotton effects. The positive exciton coupling observed for compound **13a** indicated a positive dihedral angle ∠$NOC_\alpha C_O$ and thus a right-handed turn conformation. This result correlates well with the ab initio calculation,[20] which predicted the mirror images of **1A** and **1B** as the most stable conformations.

The solvent effects on the conformations of D-α-aminoxy acid diamides were examined by CD spectroscopy. The CD spectra of compound **13a** at 0.75 mM in cyclohexane, dichloromethane, dioxane, acetonitrile, and methanol are shown in Figure 6a. Similar curves were observed in different solvents, but the Cotton effects (originating from dipole−dipole interactions between the two chromophores) showed greatly enhanced amplitudes going from polar solvents to nonpolar solvents: $\Delta\epsilon_{261} = +10.1$ and $\Delta\epsilon_{235} = -4.5$ in MeOH, whereas $\Delta\epsilon_{261} = +16$ and $\Delta\epsilon_{239} = -13.6$ in cyclohexane. This is because the long axis transitions of the *p*-chlorophenyl chromophores coupled much more efficiently in nonpolar solvents.

The effect of side chains on the chiral N−O turn structure was also probed by CD methods. The CD spectra of diamides **13a**−**e** (Figure 6b) showed strong positive exciton coupling with maximum peaks around 260 nm and minimum peaks around 235 nm, indicating that all five diamides of D-configurations adopted the right-handed N−O turn structures though the side chains were different. Therefore, we conclude that the conformation of the chiral N−O turn is determined by the chirality

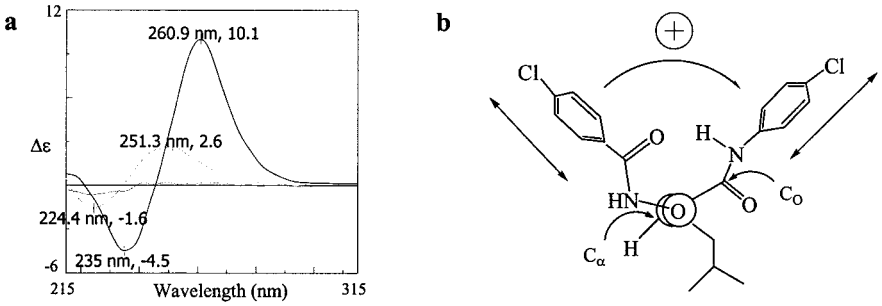


Figure 5. (a) Circular dichroism (CD) spectra of compounds **13a** (—), **15** (- - -), and **16** (···) taken at 25 °C at 0.75 mM concentration in MeOH. (b) Diagram showing a conformation of the right-handed screwness with a positive dihedral angle ∠$NOC_\alpha C_O$.

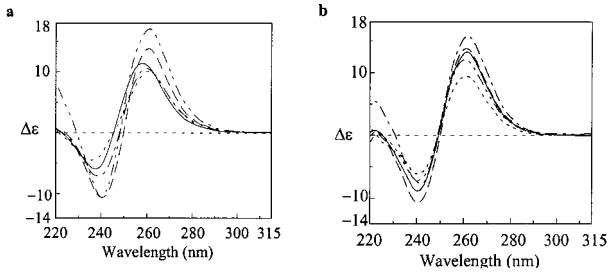


Figure 6. (a) Diamide **13a** at 0.75 mM in the following solvents: cyclohexane (- - —), CH_2Cl_2 (— ·· —), CH_3CN (—), dioxane (— — —), CH_3OH (- - -). (b) CD data of diamides **13a**−**e** at 0.75 mM in CH_2Cl_2: **13a** (— ·· —), **13b** (— — —), **13c** (— — —), **13d** (—), **13e** (- - -).

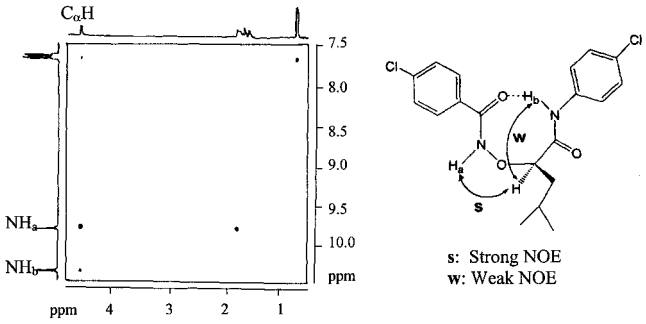


Figure 7. 2D ROESY spectrum of compound **13a** (5 mM in $CDCl_3$ at 10 °C).

of the α-aminoxy acid residue but not by the nature of the side chains.

2D ROESY[30] Study of Compound 13a. Two-dimensional rotating-frame Overhauser effect spectroscopy (2D ROESY) of compound **13a** (5 mM in $CDCl_3$) at 10 °C showed a strong nuclear Overhauser effect (NOE) between NH_a and $C_\alpha H$ but a weak NOE between NH_b and $C_\alpha H$, indicating that compound **13a** adopted a folded structure (Figure 7). According to the calculation results,[20] in conformation **1A**, the distance between NH_a and $C_\alpha H$ was 2.7 Å, whereas that between $C_\alpha H$ and NH_b was 3.4 Å. But for conformation **1B**, the distance between NH_a and $C_\alpha H$ was similar to that between NH_b and $C_\alpha H$. The observed NOE pattern indicated that compound **13a** should adopt the mirror image conformation of **1A** in solution.

Hydrogen Bonding Geometry Studied by X-ray Crystallography. D-α-Aminoxy acid diamides adopted a right-handed N−O turn structure in solution as determined by 1D and 2D NMR, FT-IR, and CD spectroscopic methods. Such a novel turn structure was also observed

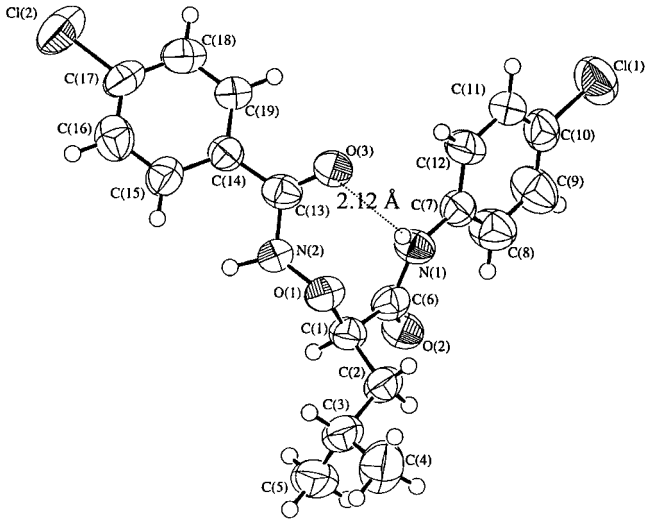


Figure 8. ORTEP view of compound **13a**.

in the solid state as revealed by X-ray structural analysis. Single crystals of compound **13a** were grown in dichloromethane solution, and its X-ray structure is shown in Figure 8.

As noted below, good agreements were found between the X-ray structure of compound **13a** and the calculated structure **1A**.[20]

An intramolecular eight-membered-ring hydrogen bond N(1)H(1)···O(3)═C(13) was identified in the X-ray structure by the short H(1)···O(3) distance (2.12 Å), correlating quite well with the calculation result (2.10 Å). Statistical surveys of crystallography data suggest that the optimum hydrogen bond distance is approximately 1.9 Å for H···O.[31]

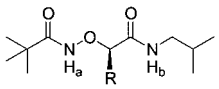
The *p*-chlorophenyl group and the adjacent amide group were found to be coplanar. Besides, the amide bonds were in the *s*-trans conformation.

The dihedral angle ∠N(2)O(1)C(1)C(6) was +78.5° in the X-ray structure, comparable to the calculation result of +78.4°, which suggests that the diamide **13a** adopted a right-handed turn conformation.

The dihedral angle ∠N(2)O(1)C(1)C(2) was −163.5° in the X-ray structure, showing that the isobutyl group was almost anti to the N−O bond. Both the ab initio calculation and 2D ROESY study indicated that such a structure was the most stable conformation.

(30) Bothner-by, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811−813.
(31) Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97.

Table 2. Upfield Chemical Shift Values (ppm) of Amide Protons in Compounds 17−19 at Room Temperature (1 mM in CD_2Cl_2)



17 R = H
18 R = CH_2Ph
19 R = $CH_2CH(CH_3)_2$

diamide	δ_{H_a} (ppm)	δ_{H_b} (ppm)
17	8.51	8.36
18	7.94	8.32
19	8.24	8.06

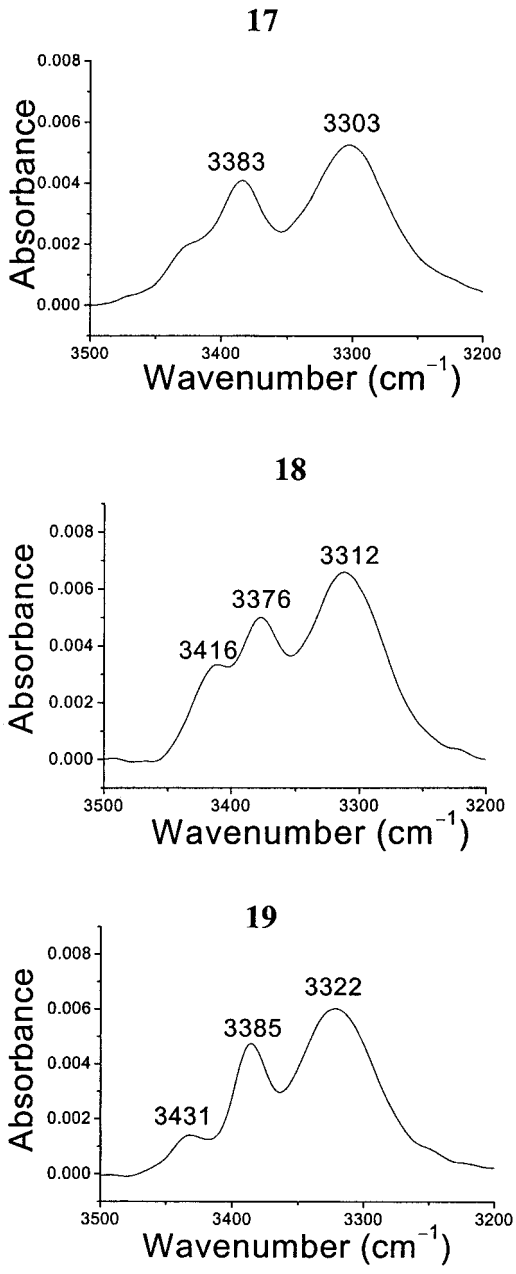


Figure 9. N−H stretch region of FT-IR spectra for compounds **17**−**19** (1 mM in CH_2Cl_2 at room temperature).

Comparison of the Stability of N−O Turns with or without an α-Substituent. To compare the relative stability of the chiral N−O turns carrying an α-substituent with that formed from α-aminoxyacetic acids, diamides **17**−**19** with identical N- and C-terminal groups were prepared. ^{1}H NMR dilution studies of diamides **17**−**19** in CD_2Cl_2 revealed similar upfield chemical shift values (δ 8.06−8.36) of the amide proton H_b in all three compounds (Table 2). In addition, the FT-IR spectra of the N−H stretch region of compounds **17**−**19** showed similar absorption patterns (Figure 9). Therefore, we concluded that N−O turns, with or without an α-substituent, have comparable stabilities in non-hydrogen-bonding solvents. This is mainly due to the conformational constraint of the N−O bond.

Conclusion

In this paper, chiral α-aminoxy acids of various side chains were synthesized in high optical purity starting from chiral α-amino acids. A novel N−O turn with an intramolecular eight-membered-ring hydrogen bond was formed in peptides containing chiral α-aminoxy acids. The hydrogen bonding geometry of the chiral N−O turn was established by NMR, FT-IR, and CD methods as well as by X-ray crystallography and is consistent with ab initio calculation results. Right-handed N−O turns were preferred for D-aminoxy acid residues and were independent of side chains. The rigid chiral N−O turns should have great potential as foldamers in molecular design.

Experimental Section

Characterization Data for D-Methyl 2-*N*-Benzyloxycarbonyl-aminoxy-3-methyl Butanoate (6a): colorless oil; $[\alpha]^{20}_D = +98.5°$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.35 (m, 5H), 5.17 (d, J = 3.4 Hz, 2H), 4.25 (d, J = 4.8 Hz, 1H), 3.76 (s, 3H), 2.09−2.20 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.6, 156.9, 135.5, 128.6, 128.5, 128.3, 88.7, 67.6, 51.9, 30.4, 18.6, 17.4; IR (CH_2Cl_2) 3380 (N−H), 1746 (C=O) cm^{-1}; FABMS *m*/*z* 282 ($M^+ + 1$).

Characterization Data for D-Methyl 2-*N*-Benzyloxycarbonyl-aminoxy-3-methyl Pentanoate (6b): colorless oil; $[\alpha]^{20}_D = +90.2°$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.35 (m, 5H), 5.17 (d, J = 3.4 Hz, 2H), 4.46 (dd, J = 3.8, 9.7 Hz, 1H), 3.75 (s, 3H), 1.86−1.97 (m, 1H), 1.65−1.75 (m, 1H), 1.48−1.55 (m, 1H), 0.95 (d, J = 5.7 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.6, 156.9, 135.4, 128.6, 128.5, 128.4, 82.6, 67.7, 52.1, 39.8, 24.5, 23.1, 21.5; IR (CH_2Cl_2) 3383 (N−H), 1747 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 295 (M^+); HRMS (EI, 20 eV) calcd for $C_{15}H_{21}NO_5$ (M^+) 295.1240, found 295.1241.

Characterization Data for D-Methyl 2-*N*-Benzyloxycarbonyl-aminoxy-3-phenyl Propanoate (6c): white solid; mp 74−75 °C; $[\alpha]^{20}_D = +49.0°$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.20−7.39 (m, 10H), 5.12 (d, J = 1.9 Hz, 2H), 4.68 (dd, J = 5.3, 7.0 Hz, 1H), 3.70 (s, 3H), 3.12 (dd, J = 4.0, 7.0 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.3, 156.9, 135.7, 135.4, 129.3, 128.6, 128.5, 128.4, 128.3, 127.0, 84.4, 67.6, 52.1, 37.1; IR (CH_2Cl_2) 3379 (N−H), 1751 (C=O) cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 329 (M^+); HRMS (EI, 20 eV) calcd for $C_{18}H_{19}NO_5$ (M^+) 329.1263, found 329.1274.

L-2-Hydroxy-3-phenylpropionic Acid (7c). L-Phenylalanine (5 g, 0.03 mol) was dissolved in dilute hydrochloric acid (130 mL, 0.5 N) at 0 °C. Sodium nitrite (6.2 g, 0.09 mol) was added. The mixture was allowed to stir at 0 °C for 6 h. The solution was transferred into a separating funnel and extracted with diethyl ether. The combined organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo, and then azeotroped with toluene twice to yield a yellow syrup. After removal of residual toluene under high vacuum, the residue was washed with hexane and filtered to give a white solid (2.93

g, 58%): mp 126−127 °C (lit.[32] 124.5 °C); ^{1}H NMR (270 MHz, CD_3OD) δ 7.25 (m, 5H), 4.33 (dd, J = 4.4, 8.0 Hz, 1H), 3.10 (dd, J = 4.4, 13.8 Hz, 1H), 2.91 (dd, J = 8.0, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 135.8, 129.5, 129.3, 128.7, 128.5, 127.2, 71.0, 40.2.

L-*tert*-Butyl 2-Acetyloxy-3-phenylpropanoate (9c). To compound **7c** (2 g, 12.1 mmol) was added acetyl chloride (10 mL) at 0 °C. The reaction mixture was then refluxed at 60 °C for 4 h. Excess acetyl chloride was removed under vacuum. Diethyl ether was added, and the solution was washed with water. The organic layer was dried and evaporated under vacuum to give compound **8c** (2.43 g) as a crude oil. The product was used in the next step without further purification. Compound **8c** and *tert*-butyl alcohol (1.97 g, 26.6 mmol) were dissolved in CH_2Cl_2 (30 mL), and DMAP (486 mg, 4.0 mmol) was added. Then, DCC (3.29 g, 16.0 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C. The reaction mixture was stirred at room temperature (rt) for 12 h. Then, the urea was filtered and the organic layer was washed with water. The organic layer was dried and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (15% EtOAc in *n*-hexane) to give compound **9c** as a yellow oil (2.53 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 5H), 5.09 (dd, J = 5.2, 8.2 Hz, 1H), 3.09 (m, 2H), 2.05 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.27, 168.69, 136.18, 129.38, 128.34, 126.88, 82.13, 73.37, 37.31, 27.84, 20.59.

L-*tert*-Butyl 2-Hydroxy-3-phenylpropanoate (10c). To a solution of potassium carbonate (5.04 g, 36.5 mmol) in methanol (14 mL) and water (20 mL) was added compound **9c** (3.21 g, 12.2 mmol). The resulting solution was stirred vigorously at rt for 12 h. Methanol was removed under vacuum, and the resulting aqueous solution was extracted with CH_2Cl_2 twice. The organic layer was then dried over anhydrous sodium sulfate and concentrated under vacuum to provide compound **10c** as a yellow oil (2.40 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.19 (m, 5H), 4.31 (m, 1H), 3.08 (dd, J = 4.8, 13.9 Hz, 1H), 2.93 (dd, J = 7.1, 13.6 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 137.1, 129.6, 128.6, 127.0, 82.8, 71.7, 40.9, 28.3; LRMS (EI, 20 eV) m/z 222 (M^+); HRMS (EI, 20 eV) calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1246.

D-*tert*-Butyl 2-Phthalimidoxy-3-phenylpropanoate (11c). To a solution of compound **10c** (2.57 g, 11.6 mmol), *N*-hydroxyphthalimide (1.89 g, 11.6 mmol), and triphenylphosphine (3.04 g, 11.6 mmol) in anhydrous THF (30 mL) at 0 °C under nitrogen was added diethylazodicarboxylate (2 mL, 12.7 mmol) via a syringe. The mixture was stirred overnight, and the solvent was removed in vacuo. The residue was taken up with CH_2Cl_2 and water. The organic layer was dried over anhydrous sodium sulfate and evaporated off under vacuum. The resulting residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to provide compound **11c** as a white solid (3.8 g, 89%): mp 68−70 °C; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.34; $[\alpha]^{20}_D$ = +26.4° (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.83 (m, 4H), 7.23−7.36 (m, 5H), 4.93 (t, J = 7.1 Hz, 1H), 3.31 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.2, 163.5, 135.5, 134.9, 129.9, 129.2, 128.8, 127.4, 124.0, 86.6, 83.1, 37.5, 28.1; MS (APCI) m/z 367 (M^+).

D-*tert*-Butyl 2-Phthalimidoxy-4-methylpentanoate (11a): prepared following the same procedure for compound **11c**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.30; 70% yield; white solid; mp 76−78 °C; $[\alpha]^{20}_D$ = +77.0° (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.78 (m, 4H), 4.74 (dd, J = 5.1, 9.0 Hz, 1H), 1.98 (m, 2H), 1.66 (m, 1H), 1.45 (s, 9H), 1.06 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 169.2, 163.2, 134.5, 128.9, 123.6, 84.8, 82.4, 39.9, 27.9, 24.5, 22.9, 22.0; MS (APCI) m/z 333.9 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1576, found 333.1573.

D-*tert*-Butyl 2-Phthalimidoxy-propanoate (11b): prepared following the same procedure for compound **11c**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.20; 69% yield; white solid; mp 97−98 °C; $[\alpha]^{20}_D$ = +58.3° (*c* 1.80, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.77 (m, 4H), 4.83 (q, J = 6.7 Hz, 1H), 1.61 (d, J = 6.7 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.76, 163.22, 134.49, 128.78, 123.52, 82.43, 81.68, 27.77, 16.39; IR (CH_2Cl_2) 1794 (C=O), 1739 (C=O) cm^{-1}; LRMS (EI, 20 eV) m/z 291 (M^+, 3), 111 (49), 97 (70), 89 (54), 77 (100); HRMS (EI, 20 eV) calcd for $C_{15}H_{17}NO_5$ (M^+) 291.1107, found 291.1112.

D-*tert*-Butyl 2-Phthalimidoxy-3-methylbutanoate (11d): prepared following the same procedure for compound **11c**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.23; 75% yield; white solid; mp 79−80 °C; $[\alpha]^{20}_D$ = +64.3° (*c* 1.10, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.75 (m, 4H), 4.34 (d, J = 7.4 Hz, 1H), 2.31−2.28 (m, 1H), 1.49 (s, 9H), 1.23 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 168.41, 163.13, 134.55, 128.84, 123.50, 91.43, 82.29, 30.35, 27.89, 18.39, 18.07; IR (CH_2Cl_2) 1793 (C=O), 1739 (C=O) cm^{-1}; LRMS (EI, 20 eV) m/z 319 (M^+, 3), 111 (41), 77 (100); FABMS m/z 320 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{17}H_{23}NO_5$ (M^+) 319.1420, found 319.1420.

D-*tert*-Butyl 2-Phthalimidoxy-3-methylpentanoate (11e): prepared following the same procedure for compound **11c**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.38; 83% yield; white solid; mp 85−87 °C; $[\alpha]^{20}_D$ = +43.5° (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.75 (m, 4H), 4.53 (d, J = 6.1 Hz, 1H), 2.08−2.01 (m, 1H), 1.72−1.65 (m, 1H), 1.49 (s, 9H), 1.40−1.27 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.43, 163.01, 134.36, 128.72, 123.31, 89.21, 82.09, 36.83, 27.76, 25.01, 14.34, 11.19; IR (CH_2Cl_2) 1793 (C=O), 1739 (C=O) cm^{-1}; FABMS m/z 334 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1576, found 333.1555.

D-*tert*-Butyl 2-*p*-Chlorophenylcarbonyl-aminoxy-4-methylpentanoate (12a). To a solution of **11a** (1 g, 3.00 mmol) in anhydrous methanol (10 mL) was added hydrazine hydrate (0.62 mL, 9 mmol), and the resulting mixture was stirred at rt for 1 h. The mixture was concentrated under vacuum, and 3% sodium carbonate solution (10 mL) was added. After the mixture was extracted with ether, the combined organic layer was dried over anhydrous sodium sulfate and concentrated to provide 533 mg of oil. Then, 4-chlorobenzoic acid (469 mg, 3 mmol) was added together with CH_2Cl_2 (10 mL). To this mixture were added HOBt (608 mg, 4.50 mmol) and EDCI (891 mg, 3 mmol). The reaction mixture was stirred overnight. The organic layer was washed with saturated sodium hydrogen carbonate and dilute hydrochloric acid solution. It was then dried and evaporated, and the residue was then purified by flash column chromatography (10% EtOAc in *n*-hexane) to provide compound **12a** as a white solid (780 mg, 76%): mp 105−107 °C; $[\alpha]^{20}_D$ = +51.4° (*c* 1.50, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 4.52 (dd, J = 4.1, 9.2 Hz, 1H), 2.03 (m, 1H), 1.80 (m, 2H), 1.50 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 171.88, 164.81, 138.41, 130.29, 129.02, 128.50, 127.43, 82.56, 82.33, 39.87, 28.08, 24.69, 23.13, 21.76; IR (CH_2Cl_2) 3393 (N−H) cm^{-1}; MS (APCI) m/z 341.9 (M^+); HRMS (EI, 20 eV) calcd for $C_{17}H_{24}NO_4Cl$ (M^+) 341.1394, found 341.1386.

D-*tert*-Butyl 2-*p*-Chlorophenylcarbonyl-aminoxy-propanoate (12b): prepared following the same procedure for compound **12a**; 76% yield; white solid; mp 69−70 °C; $[\alpha]^{20}_D$ = +68.6° (*c* 1.00, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.68 (dd, J = 1.9, 7.7 Hz, 2H), 7.40 (dd, J = 1.9, 7.7 Hz, 2H), 4.56 (q, J = 7.0 Hz, 1H), 1.50 (d, J = 7.0 Hz, 3H), 1.49 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.97, 165.07, 138.44, 130.25, 129.02, 128.66, 82.70, 79.67, 28.09, 16.35; IR (CH_2Cl_2) 1733 (C=O), 1690 (C=O) cm^{-1}; LRMS (EI, 20 eV) m/z 299 (M^+, 3), 243 (42), 141 (31), 139 (100); FABMS m/z 300 (M^+ + 1); HRMS (EI, 20 eV) calcd for $C_{14}H_{18}NClO_4$ (M^+) 299.0924, found 299.0938.

D-*tert*-Butyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-phenylpropanoate (12c): prepared following the same procedure for compound **12a**; 67% yield; white solid; mp 95−96 °C; $[\alpha]^{20}_D$ = +29.7° (*c* 1.02, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$)

(32) Weast, R. C. *Handbook of Chemistry and Physics*, 67th ed.; CRC Press: Boca Raton, FL, 1986−1987.

δ 10.22 (br, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.26−7.16 (m, 5H), 4.80 (t, J = 6.2 Hz, 1H), 3.18 (dd, J = 6.4, 14.4 Hz, 1H), 3.09 (dd, J = 6.2, 14.4 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.80, 165.31, 138.10, 135.35, 130.18, 129.55, 128.74, 128.24, 126.88, 83.69, 82.69, 37.19, 27.85; IR (CH_2Cl_2) 1733 (C═O), 1693 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 375 (M^+, 2), 319 (14), 171 (11), 149 (100); FABMS *m/z* 376 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{20}H_{22}NClO_4$ (M^+) 375.1237, found 375.1258.

D-*tert*-Butyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-methylbutanoate (12d): prepared following the same procedure for compound **12a**; 95% yield; white solid; mp 99−101 °C; $[\alpha]^{20}_D$ = +55.4° (*c* 1.02, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 4.34 (d, J = 4.6 Hz, 1H), 2.18−2.11 (m, 1H), 1.48 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.92 MHz, $CDCl_3$) δ 171.20, 165.21, 138.08, 130.51, 128.75, 88.00, 82.42, 30.53, 28.07, 18.38, 17.45; IR (CH_2Cl_2) 1730 (C═O), 1690 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 327 (M^+, 1), 271 (29), 155 (11), 141 (30), 139 (100); FABMS *m/z* 328 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{16}H_{22}NClO_4$ (M^+) 327.1237, found 327.1241.

D-*tert*-Butyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-methylpentanoate (12e): prepared following the same procedure for compound **12a**; 61% yield; white solid; mp 87−88 °C; $[\alpha]^{20}_D$ = +48.8° (*c* 1.10, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 4.45 (d, J = 3.4 Hz, 1H), 2.04−1.88 (m, 1H), 1.80−1.58 (m, 1H), 1.50 (s, 9H), 1.47−1.34 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.19, 164.67, 138.33, 130.38, 129.00, 128.49, 86.19, 82.49, 37.27, 28.12, 25.81; IR (CH_2Cl_2) 1730 (C═O), 1691 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 341 (M^+, 3), 285 (20), 182 (28), 139 (100); FABMS *m/z* 342 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{17}H_{24}NO_4Cl$ (M^+) 341.1394, found 341.1404.

D-*p*-Chlorophenyl 2-*p*-Chlorophenylcarbonyl-aminoxypropanoamide (13b). A solution of compound **12b** (589 mg, 1.73 mmol) in dichloromethane (5 mL) in an ice bath was treated with trifluoroacetic acid (5 mL). After being stirred at room temperature for 1 h, the reaction mixture was concentrated under vacuum and azeotroped with toluene. Then, 4-chloroaniline (220 mg, 1.73 mmol) was added together with dichloromethane (10 mL). To this mixture were added HOBt (351 mg, 2.60 mmol) and EDCI (668 mg, 2.25 mmol). The reaction mixture was stirred overnight. The organic layer was washed with a solution of saturated sodium hydrogen carbonate and dilute hydrochloric acid. It was then dried over anhydrous sodium sulfate, evaporated under vacuum, and purified by flash column chromatography (20% EtOAc in *n*-hexane) to provide compound **13b** (512 mg, 84%) as a white crystalline solid: mp 84−86 °C; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.14; $[\alpha]^{20}_D$ = +116.4° (*c* 1.10, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.51 (s, 1H), 10.22 (s, 1H), 7.71 (dd, J = 8.6, 1.8 Hz, 2H), 7.63 (dd, J = 2.0, 8.8 Hz, 2H), 7.36 (dd, J = 2.0, 8.6 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 4.52 (q, J = 7.0 Hz, 1H), 1.56 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.14, 167.61, 139.34, 136.14, 129.58, 129.17, 128.97, 128.69, 128.64, 121.32, 83.83, 17.38; IR (CH_2Cl_2) 1690 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 352 (M^+, 26), 141 (32), 139 (100); FABMS *m/z* 353 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{16}H_{14}N_2Cl_2O_3$ (M^+) 352.0381, found 352.0377.

D-*p*-Chlorophenyl 2-*p*-Chlorophenylcarbonyl-aminoxy-4-methylpentanoamide (13a): prepared following the same procedure for compound **13b**; 53% yield; white solid; mp 92−95 °C; $[\alpha]^{20}_D$ = +119.6° (*c* 2.70, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.88 (s, 1H), 7.70 (d, J = 7.7 Hz, 4H), 7.44 (d, J = 7.4 Hz, 2H), 7.28 (d, J = 9.6 Hz, 2H), 4.46 (t, J = 6.6 Hz, 1H), 1.93 (m, 1H), 1.84 (t, J = 6.8 Hz, 2H), 1.03 (d, J = 7.9 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 169.53, 168.17, 139.55, 136.48, 129.34, 129.16, 128.90, 128.61, 121.09, 86.76, 40.83, 24.95, 23.24, 21.77; IR (CH_2Cl_2) 3339, 3313, 3303, 3193 cm^{-1}; MS (APCI) 395.2 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{19}H_{20}N_2O_3Cl_2$ (M^+) 394.0851, found 394.0851.

D-*p*-Chlorophenyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-phenylpropanoamide (13c): prepared following the same procedure for compound **13b**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.15; 65% yield; white solid; mp 56−57 °C; $[\alpha]^{20}_D$ = +150.1° (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.82 (s, 1H), 7.67 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.38−7.26 (m, 4H), 4.55 (dd, J = 3.0, 10.5 Hz, 1H), 3.45 (dd, J = 3.0, 14.6 Hz, 1H), 3.05 (dd, J = 10.5, 14.6 Hz, 1H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 168.06, 167.45, 139.41, 137.17, 136.37, 129.47, 129.31, 129.22, 128.93, 128.83, 128.46, 128.43, 127.14, 121.14, 89.45, 38.06; IR (CH_2Cl_2) 3339 (br, N−H), 3302 (br, N−H), 3272 (br, N−H), 1686 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 428 (M^+, 28), 260 (31), 258 (100); FABMS *m/z* 429 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{22}H_{18}N_2Cl_2O_3$ (M^+) 428.0694, found 428.0694.

D-*p*-Chlorophenyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-methylbutanoamide (13d): prepared following the same procedure for compound **13b**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.18; 82% yield; white solid; mp 186−187 °C; $[\alpha]^{20}_D$ = +170.0° (*c* 1.04, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 9.13 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 4.24 (d, J = 4.7 Hz, 1H), 2.47−2.37 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.80, 167.96, 139.35, 136.39, 129.23, 128.89, 128.81, 128.67, 121.23, 92.32, 31.06, 19.41, 16.50; IR (CH_2Cl_2) 3376 (br, N−H), 3345 (br, N−H), 3301 (br, N−H), 3270 (br, N−H), 1687 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 380 (M^+, 37), 139 (100); FABMS *m/z* 381 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{18}H_{18}N_2Cl_2O_3$ (M^+) 380.0694, found 380.0698.

D-*p*-Chlorophenyl 2-*p*-Chlorophenylcarbonyl-aminoxy-3-methylpentanoamide (13e): prepared following the same procedure for compound **13b**; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.35; 66% yield; white solid; mp 40−42 °C; $[\alpha]^{20}_D$ = +53.4° (*c* 1.02, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 9.85 (s, 1H), 7.68 (d, J = 6.6 Hz, 2H), 7.65 (d, J = 6.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 4.35 (d, J = 3.0 Hz, 1H), 2.13−1.98 (m, 1H), 1.62−1.52 (m, 1H), 1.47−1.33 (m, 1H), 0.97−0.90 (m, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 169.52, 167.93, 139.26, 136.20, 129.47, 129.14, 128.92, 128.68, 121.36, 90.62, 37.76, 26.42, 13.52, 11.89; IR (CH_2Cl_2) 3445 (br, N−H), 3410 (br, N−H), 3370 (br, N−H), 3345 (br, N−H), 1727 (C═O), 1687 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 394 (M^+, 28), 224 (26), 154 (35), 139 (100); FABMS *m/z* 395 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{19}H_{20}N_2Cl_2O_3$ (M^+) 394.0851, found 394.0854.

D-*p*-Chlorophenyl 2-Phthalimidoxy-4-methylpentanoamide (14). A solution of **11a** (1.5 g, 4.5 mmol) in dichloromethane (5 mL) in an ice bath was treated with trifluoroacetic acid (5 mL). After being stirred at room temperature for 1 h, the reaction mixture was concentrated under vacuum and azeotroped with toluene. Then, 4-chloroaniline (574 mg, 4.5 mmol) was added together with dichloromethane (10 mL). To this mixture were added HOBt (790 mg, 5.85 mmol) and EDCI (1.35 g, 4.55 mmol). The reaction mixture was stirred overnight. The organic layer was washed with a solution of saturated sodium hydrogen carbonate and dilute hydrochloric acid. It was then dried over anhydrous sodium sulfate, evaporated under vacuum, and purified by flash column chromatography (20% EtOAc in *n*-hexane) to provide compound **14** as a white solid (1.29 g, 74%): mp 118−120 °C; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f = 0.32; $[\alpha]^{20}_D$ = +174.6° (*c* 1.30, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.78 (m, 4H), 7.76 (d, J = 8.9 Hz, 2H), 7.26 (d, J = 8.9 Hz, 2H), 4.85 (dd, J = 3.8, 9.0 Hz, 1H), 2.18 (m, 1H), 2.84 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.96, 164.40, 136.23, 135.29, 129.55, 129.08, 128.72, 124.17, 121.23, 87.12, 41.93, 24.94, 23.39, 21.84; IR (CH_2Cl_2) 3353 (N−H), 1792 (C═O), 1736 (C═O), 1686 (C═O) cm^{-1}; LRMS (EI, 20 eV) *m/z* 386 (M^+, 3), 153 (55), 136 (53), 77 (100); HRMS (EI, 20 eV) calcd for $C_{20}H_{19}N_2O_4Cl$ (M^+) 386.1033, found 386.1031.

D-*p*-Chlorophenyl 2-*tert*-Butylcarbonyl-aminoxy-4-methylpentanoamide (15). To a solution of **14** (472 mg, 1.22 mmol) in anhydrous methanol (5 mL) was added hydrazine

hydrate (0.25 mL, 3.66 mmol), and the resulting mixture was stirred at rt for 1 h. The mixture was concentrated under vacuum, and 3% sodium carbonate solution was added. The mixture was extracted with ether. The combined organic layer was dried over anhydrous sodium sulfate and concentrated to provide a white solid **14a** (225 mg). Compound **14a** was used in the next step without further purification. To a solution of compound **14a** in dichloromethane (10 mL) were added pyridine (0.133 mL, 1.59 mmol) and trimethylacetyl chloride (0.104 mL, 1.22 mmol) at 0 °C. The mixture was then allowed to stir at rt for 5 h. The mixture was washed with dilute hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to provide compound **15** (280 mg, 67%) as a white solid: mp 165−167 °C; $[\alpha]^{20}_D = +127.7°$ (*c* 1.80, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.41 (s, 1H), 7.66 (d, $J = 8.9$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 4.33 (t, $J = 6.6$ Hz, 1H), 1.89 (m, 1H), 1.79 (t, $J = 6.6$ Hz, 2H), 1.21 (s, 9H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.99 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 179.55, 169.64, 136.62, 128.98, 128.84, 121.11, 86.32, 40.78, 38.25, 27.06, 24.88, 23.26, 21.77; IR (CH_2Cl_2) 3378, 3293, 3264, 3191 cm^{-1}; MS (APCI) 341.2 ($M^+ + 1$); HRMS (EI, 20 eV) calcd for $C_{17}H_{25}N_2O_3Cl$ (M^+) 340.1554, found 340.1548.

D-Isobutyl 2-*p*-Chlorophenylcarbonyl-aminoxy-4-methylpentanoamide (16). A solution of **12a** (580 mg, 1.7 mmol) in dichloromethane (5 mL) at 0 °C was treated with trifluoroacetic acid (5 mL). After being stirred at rt for 1 h, the reaction mixture was concentrated under vacuum and azeotroped with toluene. It was then dissolved in dichloromethane (10 mL), followed by addition of isobutylamine (0.34 mL, 3.4 mmol). To this mixture were added HOBt (344 mg, 2.55 mmol) and EDCI (555 mg, 1.87 mmol). The reaction mixture was stirred overnight. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to provide compound **16** (460 mg, 80%) as a white solid: mp 99−102 °C; $[\alpha]^{20}_D = +31.2°$ (*c* 1.80, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.22 (t, $J = 5.7$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 2H), 4.31 (dd, $J = 3.6$, 9.1 Hz, 1H), 2.82 (m, 2H), 1.76 (m, 1H), 1.70 (m, 2H), 0.77 (m, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.49, 166.94, 139.10, 129.79, 129.40, 129.27, 129.23, 128.59, 85.61, 47.08, 41.41, 28.69, 25.04, 23.57, 21.99, 20.43; IR (CH_2Cl_2) 3433, 3380, 3341 cm^{-1}; MS (APCI) 341.2 (M^+); HRMS (EI, 20 eV) calcd for $C_{17}H_{26}N_2O_3Cl$ (M^+) 341.1632, found 341.1646.

Compound 17: white crystalline solid; mp 62−65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.50 (br s, 1H), 4.34 (s, 2H), 3.12 (t, $J = 6.4$ Hz, 2H), 1.85−1.80 (m, 1H), 1.21 (s, 9H), 0.93 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.48, 168.80, 75.89, 46.61, 37.98, 28.37, 27.07, 20.14; IR (CH_2Cl_2) 3383 (br), 3303 (br), 2966, 1687, 1679 cm^{-1}; LRMS (CI) *m*/*z* 231 ($M^+ + 1$); HRMS (CI) calcd for $C_{11}H_{22}N_2O_3$ (M^+) 230.1630, found 230.1630.

Compound 18: white crystalline solid; mp 97−100 °C; $[\alpha]^{20}_D$ +64.4° (*c* 1.09, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.96 (s, 1H), 7.38−7.25 (m, 5H), 4.33 (dd, $J =$ 10.4, 3.0 Hz, 1H), 3.39 (dd, $J = 14.5$, 3.0 Hz, 1H), 3.18−3.00 (m, 2H), 2.94 (dd, $J = 10.4$, 14.5 Hz, 1H), 1.84−1.75 (m, 1H), 1.05 (s, 9H), 0.92 (d, $J = 3.9$ Hz, 3H), 0.89 (d, $J = 3.9$ Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 177.65, 169.79, 137.53, 129.46, 128.61, 126.85, 88.35, 46.66, 38.10, 37.84, 28.37, 26.89, 20.13; IR (CH_2Cl_2) 3416 (br), 3376 (br), 3312 (br), 2969, 1684, 1611 cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 320 (M^+, 1), 248 (2), 204 (100); HRMS (EI) calcd for $C_{18}H_{28}N_2O_3$ (M^+) 320.2100, found 320.2101.

Compound 19: white crystalline solid; mp 112−114 °C; $[\alpha]^{20}_D$ +64.2° (*c* 0.89, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.12 (br s, 1H), 4.26 (dd, $J = 7.7$, 5.5 Hz, 1H), 3.14−3.09 (m, 1H), 3.04−2.99 (m, 1H), 1.89−1.77 (m, 2H), 1.70−1.68 (m, 2H), 1.20 (s, 9H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.91 (d, $J = 5.6$ Hz, 3H), 0.92 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.40, 171.56, 85.47, 46.55, 41.01, 38.11, 28.45, 27.12, 24.78, 23.30, 21.81, 20.18, 20.15; IR (CH_2Cl_2) 3431 (br), 3385 (br), 3322 (br), 2964, 1687, 1659 cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 286 (M^+, 20), 214 (18), 131 (100); HRMS (EI) for $C_{15}H_{30}N_2O_3$ (M^+) calcd 286.2256, found 286.2182.

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Supporting Information Available: General experimental data; HPLC analysis of chiral α-aminoxy acids **6a**−**c**, **11a**, **11c**, and **11d**; ^{1}H NMR dilution study of compounds **17**−**19**; and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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