Stereoselective Synthesis of Freidinger Lactams Using Oxaziridines Derived from Amino Acids

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Conformationally restrained dipeptidyl lactams are building blocks for the synthesis of peptidomimetics, including Freidinger lactams (Figure 1). Few synthetic methodologies toward such moieties allow for incorporation of a stereodefined substituent on the ring nitrogen (i.e., corresponding to an amino acid side chain). Enantiopure Freidinger lactams were obtained by (1) condensation of *(S)-tert*-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones with commercially available α-amino esters, (2) oxidation of the resulting imines with *m*-CPBA to give spirocyclic oxaziridines, and (3) photorearrangement. Conformational analyses of seven- and eight-membered dipeptidyl lactams by NMR and by X-ray crystallography are described. The utility of this chemistry was illustrated by the synthesis of potential inhibitors of angiotensin converting enzyme (ACE).

Endogenous peptide hormones and neurotransmitters represent an important and still largely untapped reservoir of diverse lead molecules for drug development.[1] Problems such as poor solubility, poor gastrointestinal absorption, multiple physiological effects, and short biological half-lives have limited the direct clinical utility of most endogenous peptides.[2] The design and synthesis of conformationally restricted peptidomimetics is an important approach toward improving the potency, selectivity, and metabolic stability of peptide hormones and neurotransmitters.[3] Among the numerous strategies toward the conformational restriction of peptides, incorporating the backbone into a "Freidinger" lactam structure[4] (Figure 1) has proven useful in the design of a variety of medicinally relevant targets[5] but especially peptidase/protease inhibitors.[6] Such cyclization of the peptide backbone[7] fixes the amide bond in the trans rotameric form, places severe limitations on ψ_1 rotation, and would be expected to bias neighboring ϕ_1 and ϕ_2 torsional angles.

Several different synthetic strategies have been developed toward Freidinger lactams (loosely defined to encompass monocyclic γ-, δ-, and ϵ-lactams), including some

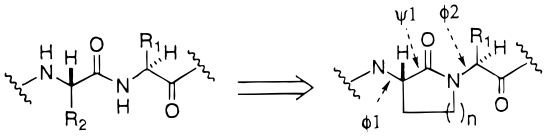

Figure 1. Conformational restriction of the peptide backbone via a Freidinger lactam.

stereoselective methods that allow control over the C-3 center (amino substituent) or the glycyl side chain (R_1 in Figure 1).[4−6,8] However, no one method has proved completely facile for the stereoselective synthesis of Freidinger lactams of various ring sizes containing a spectrum of C-terminal amino acid residues. An ideal method would (1) be applicable to lactams of various sizes, (2) allow the installation of potentially expensive and/or scarce amino acid moieties late in the scheme, permitting divergence to a number of amino acid substitutions (and obviously relevant to combinatorial ap-

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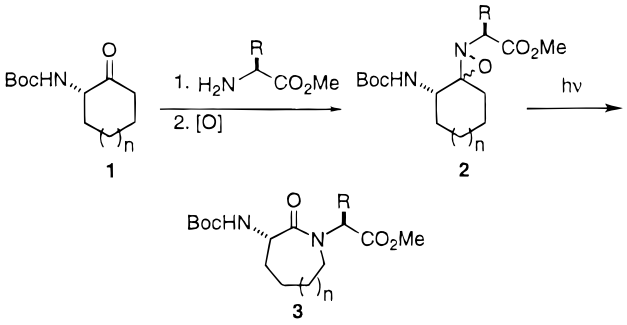
Scheme 1



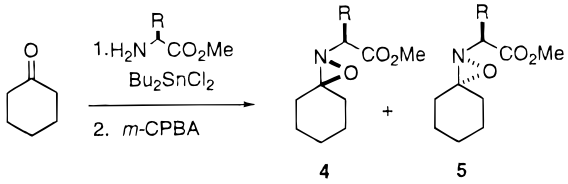
proaches), (3) incorporate protection schemes consonant with standard peptide chemistry, and (4) allow control over relative and absolute stereochemistry. The stereoselective synthesis of chiral lactams from cyclic ketones using spirocyclic oxaziridines has become established as a potent tool in ring-expansion chemistry.[9] We thought an oxaziridine-mediated approach to Freidinger lactams could potentially address all of the above criteria.

Our general synthetic strategy is depicted in Scheme 1. Condensation of enantiopure *(S)-tert*-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones **1** with commercially available α-amino esters and subsequent oxidation of the imines with *m*-CPBA should form oxaziridines **2** in which the N-substituent is oriented trans to the more highly substituted carbon for steric reasons. Oxaziridines are known to rearrange to lactams under photochemical conditions so that the carbon anti to the nitrogen lone pair of electrons migrates predominantly.[9] Therefore, the stereochemical relationship of oxaziridines **2** should dictate the formation of the desired regioisomeric lactams **3** upon photorearrangement. *No other kind of known nitrogen insertion process could be expected to reliably provide lactams of this regiochemical type.* In a preliminary communication, we reported the formation of stereodefined Freidinger lactams **3** utilizing a variety of α-amino esters.[10] Here we (1) describe this chemistry in detail, (2) discuss the stereochemistry of the oxidation of amino ester-derived imines in general, (3) provide X-ray crystallographic structures for seven- and eight-membered Freidinger lactams, and (4) illustrate the utility of this chemistry in the synthesis of potential angiotensin-converting enzyme (ACE) inhibitors.

Results and Discussion

Stereochemical Preferences of Oxaziridine Formation Using α-amino esters. In order to establish some general principles governing the oxidation of imines derived from α-amino esters, we examined oxaziridine formation using cyclohexanone and *(R)*-3-methylcyclohexanone. Condensation of L-α-amino methyl esters with cyclohexanone in the presence of catalytic dibutyltin dichloride[11] and subsequent oxidation of the imines with *m*-CPBA provided oxaziridines **4** and **5** in good yields.

Table 1. Stereochemistry of Oxaziridine Formation From Cyclohexanone and Selected α-Amino Esters



			oxaziridines		
entry	R	amino ester	products	yield (%)	ratio
1	CH_2Ph	L-Phe-OMe	**4a**/**5a**	79	>95:5[a,b]
2	*i*-Bu	L-Leu-OMe	**4b**/**5b**	80	88:12
3	*i*-Pr	L-Val-OMe	**4c**/**5c**	80	>95:5[a,b]
4	CH_2CO_2Me	L-Asp(OMe)-OMe	**4d**/**5d**	80	54:46[a,b,c]
5	CH_2OCH_2Ph	L-Ser(OBn)-OMe	**4e**/**5e**	67	60:40[b,c]

[a] Ratios were determined by 500 MHz ^{1}H-NMR examination of the crude reaction mixture. [b] Approximate ratios were determined by isolation of pure isomers. [c] Stereochemical assignments not made.

The results of these experiments (Table 1) clearly indicate a preference for *like* stereochemistry when the α-amino ester side chain is an unfunctionalized hydrophobic group (entries 1−3; the direction of attack was assigned in analogy to experiments carried out with (*R*)-3-methylcyclohexanone, as described below). High stereochemical preferences were seen using phenylalanine and valine methyl esters (entries 1 and 3), in which only one diastereomer was observed within the limits of ^{1}H-NMR detection. Oxaziridine formation via leucine methyl ester (entry 2) was slightly less selective although the diastereomeric ratio was still acceptably high. The high preference for like stereochemistry is similar to that observed with α-methylbenzylamine.[12] In sharp contrast, stereochemical preferences of oxaziridine formation were essentially absent when the functionized aspartate and serine methyl esters were employed (entries 4 and 5). The reasons for the differences between functionalized and unfunctionalized amino ester side chains are probably related to the diminished size differential between CH_2CO_2Me/CO_2Me vs CH_2Ph/CO_2Me. Whatever the reason, similar differences were also observed in analogous experiments with protected 2-aminocyclohexanone **1** (vide infra).

The preferential formation of *like*-configured oxaziridines was established by analyzing reactions of the imine derived from Phe-OMe and *(R)*-3-methylcyclohexanone (Scheme 2). Oxaziridine formation with L-phenylalanine methyl ester under the standard conditions provided predominantly one diastereomer of **6** (ratio ca. 7:1). This major diastereomer photorearranged to 4-methylcaprolactam **7**; hence, the nitrogen lone pair of electrons of **6** is oriented trans to the migrating C-8 carbon. This

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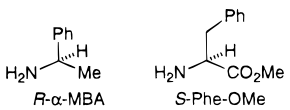
(12) The *unlike* product is preferred when α-methylbenzylamine is employed.[9] However, the preference for like stereochemistry using phenylalanine methyl ester (Phe-OMe) is probably a consequence of the rules for prioritizing substituents in the Cahn−Prelog−Ingold system; hence, L-Phe-OMe (i.e., (*S*)-Phe-OMe) can be superimposed onto (*R*)-α-methylbenzylamine better than it can be superimposed onto (*S*)-α-methylbenzylamine (see structures below). The use of either of these two amines results in a preference for *S* stereochemistry at N-2 of the resulting oxaziridine.



Scheme 2

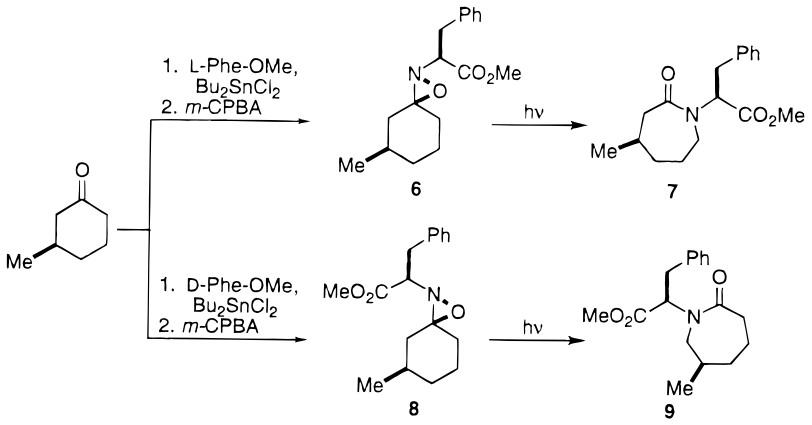
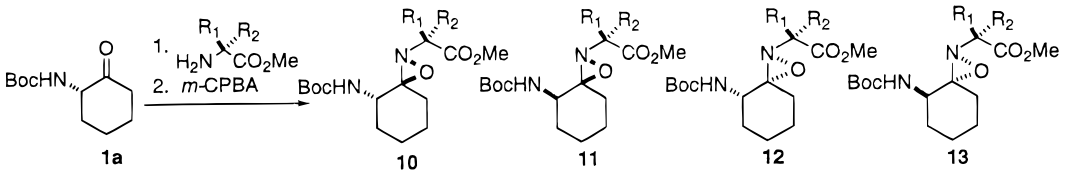


Table 2. Oxaziridine Formation from (*S*)-Boc-2-Aminocyclohexanone and α-Amino Esters



entry	amino ester	R_1	R_2	products	yield (%)	ratio
1	L-Phe-OMe	CH_2Ph	H	**10a**	72	>95:5[a]
2	D-Phe-OMe	H	CH_2Ph	**12b/13b**[b]	61	93:7[c]
3	L-Leu-OMe	$CH_2CH(CH_3)_2$	H	**10c/11c**	62	77:23[c]
4	D-Leu-OMe	H	$CH_2CH(CH_3)_2$	**10d/12d**	60	50:50[a]
5	L-Val-OMe	$CH(CH_3)_2$	H	**10e/11e/12e**	66	48:39:13[a,c]
6	L-Asp(OMe)-OMe	CH_2CO_2Me	H	**10f** + **12f/11f** or **13f**	70	57:43[a,c]

[a] Ratio estimated by ^{1}H NMR. [b] Note that **12b** is *ent*-**11a** and **13b** is *ent*-**10a**. [c] Ratio estimated by separation of isomers.

information, in combination with the known[9,13] preference for equatorial approach of oxidant to imines derived from enantiopure 3- and 4-substituted cyclohexanones, provided a complete stereochemical assignment to **6**. In contrast, condensation of *(R)*-3-methylcyclohexanone with D-phenylalanine methyl ester afforded oxaziridine **8** as the major diastereomer, with photorearrangment yielding 5-methylcaprolactam **9**. The clear stereochemical assignments of oxaziridines **6** and **8** allowed us to assign the configurations of the oxaziridines in Table 1 by analogy. The experiments using *(R)*-3-methylcyclohexanone demonstrated that the use of α-amino esters is compatible with both oxaziridine formation and photorearrangment, providing the desired products in good yields. Furthermore, no compromise of the amino ester stereocenter was noted during oxaziridine formation under the conditions employed. This was evident by the formation of compounds **6** and **8** as single diastereomers: if the α-center had epimerized, some of the same products would have been obtained in the two different experiments. Retention at this stereocenter is essential for obtaining enantiopure Freidinger lactams.

Formation of Freidinger-Type Dipeptidyl Lactams. We have previously detailed the synthesis of enantiopure *(S)-tert*-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones **1** from cycloalkene oxides.[14] The key step of the route is cycloalkene oxide ring opening with *(R)*-α-methylbenzylamine and chromatographic separation of the resulting diastereomeric amino alcohols. Condensation between ketone **1a** and L-phenylalanine methyl ester and oxidation via *m*-CPBA occurred smoothly to afford a single diastereomeric oxaziridine **10a** (Table 2, entry 1). The standard conditions entailed the use of 20 mol % dibutyltin dichloride,[11] 2 equiv of sodium bicarbonate, and a high proportion of pulverized 5 Å molecular sieves. This protocol was found to be important both for optimizing the yield of the reaction and for preventing epimerization of the C-4 (BocNH substituted) stereocenter. For instance, performing the oxaziridine synthesis under toluene reflux and without tin catalyst or bicarbonate led to the formation of diastereomers **10a** and **11a** in an essentially 1:1 ratio.

The stereochemical assignments of oxaziridines **10a** and **11a** were made by several considerations. One is that **10a** and **11a** photorearranged to diastereomeric lactams **14a** and **15a**, respectively (Table 3, entries 1 and 2). Therefore, for both **10a** and **11a**, the lone pair of electrons on the oxaziridine ring nitrogen is anti to the migrating C-8 methylene group, and the amino ester moiety is trans to the bulky Boc-protected amino substituent as expected. This notion was corroborated by ^{13}C-NMR analysis: the C-8 peaks of both **10a** and **11a** have chemical shift values of ca. 27 ppm. Chemical shifts in this region correlate with carbons anti to the nitrogen lone pair electrons.[15]

The stereochemical assignment of oxaziridine **11a** was additionally supported by the observation of an unusually upfield proton (0.42 ppm) in the ^{1}H-NMR spectrum of this compound. Coupling constants and data from COSY and

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(14) Aubé, J.; Wolfe, M. S.; Yantiss, R. K.; Cook, S. M.; Takusagawa, F. *Synth. Commun.* **1992**, *22*, 3003−3012.

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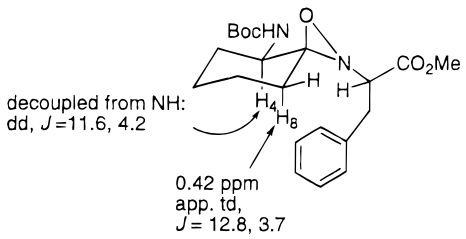


Figure 2. Proposed conformation of oxaziridine **11a**.

HETCOR NMR experiments were consistent with the notion that this signal comes from the proton bonded to C-8. This peak is an apparent doublet of triplets, with two large and coincidentally identical coupling constants of 12.8 Hz (one axial−axial coupling and one geminal coupling) and one small coupling constant of 3.7 Hz (axial−equatorial coupling). In addition, decoupling experiments revealed that H-4 is axial and, by elimination, the carbamate substituent is equatorial (the overall spectrum is consistent with the cyclohexane ring being in a well-behaved chair conformation). Molecular models show that only diastereomer **11a**, which is expected to exist largely with the α-H occupying the inside position shown, can obtain a conformation where the axial H-8 is shielded via a ring current effect of the phenyl group (Figure 2). We have previously observed similar shifts due to anisotropy in a series of oxaziridines derived from substituted benzylamines.[16]

In contrast to oxaziridine formation from ketone **1a** and L-phenylalanine methyl ester, the D-isomer of this amino ester gave lower yields and some compromise of the stereocenter at C-3 (Table 2, entry 2; the assignments were facilitated by the fact that the minor isomer formed in this experiment was the enantiomer of **10a**). The model experiments with cyclohexanone and *(R)*-3-methylcyclohexanone established a clear preference for like stereochemistry when phenylalanine methyl ester is employed (Scheme 2). We hypothesize that oxaziridine formation using ketone **1a** and the D-isomer of this amino ester is disadvantaged by the fact that equatorial attack (*β* attack) occurs from the opposite face as *like* attack (α attack); i.e., the two stereocontrolling events are mismatched (Figure 3a). In contrast, oxaziridine formation with **1a** and L-Phe-OMe methyl ester represents a case of matched stereocontrol as both equatorial attack and *like* attack occur from the *β* face (Figure 3b). This mismatching of stereochemistry leads to a lower yield and compromise of the C-3 stereocenter compared with the same reaction with the L amino ester.

We drew similar conclusions from analogous experiments with L- versus D-leucine methyl ester. Oxaziridines derived from L-leucine methyl ester were formed in somewhat lower yields and with considerable compromise of C-3 stereointegrity in comparison with L-phenylalanine methyl ester (Table 2, cf. entries 1 and 3).[17] Nevertheless, one major diastereomer formed which could be readily separated by flash chromatography, and photorearrangement of the purified **10c** provided lactam **14c** (Table 3, entry 4). In contrast to L-leucine methyl ester, when the antipodal D-Leu-OMe was used, a 1:1 mixture of diastereomeric oxaziridines was isolated (Table 2, entry 4). Photorearrangement of this 1:1 mixture (Table 3, entry 5) led to convergence on one diastereomeric lactam: therefore, the two oxaziridine diastereomers differ in N-2/C-3 stereochemistry. It appears that the intrinsic preference of leucine to direct *like* attack (Table 1, entry 2) is less able to compete with this imine's preference for equatorial attack relative to the competition observed in the phenylalanine examples.

As previously observed with cyclohexanone, oxaziridine formation from **1a** and L-aspartate dimethyl ester displayed no clear stereochemical preference (Table 2, entry 6). While a minor diastereomer could be chromatographi-

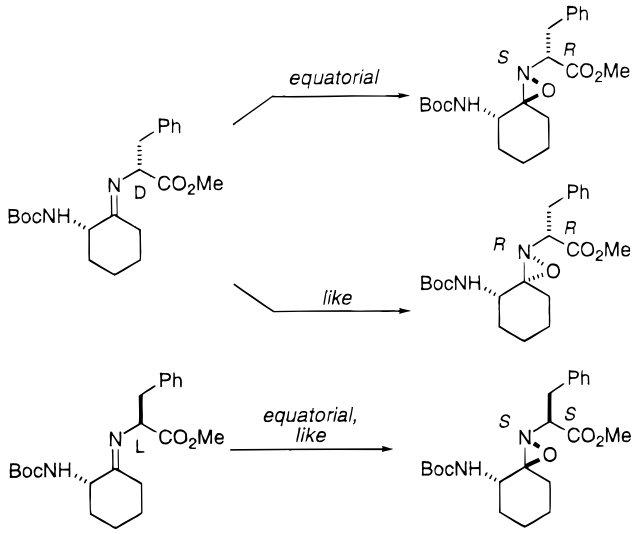
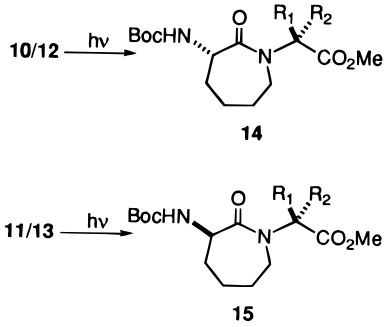


Figure 3. Stereochemical results of imine oxidation on substrates derived from D- vs L-phenylalanine.

Table 3. Photorearrangement of Oxaziridines to Freidinger Lactams



entry	oxaziridine[a]	R_1	R^2	lactam[b]	yield (%)
1	**10a**	CH_2Ph	H	**14a**	72
2	**11a**	CH_2Ph	H	**15a**	63
3	**12b**	H	CH_2Ph	**14b**	68
4	**10c**	$CH_2CH(CH_3)_2$	H	**14c**	61
5	**10d/12d**	H	$CH_2CH(CH_3)_2$	**14d**	59
6	**10e/12e**	$CH(CH_3)_2$	H	**14e**	59
7	**11e**	$CH(CH_3)_2$	H	**15e**	55
8	**10f** or **12f**[c]	CH_2CO_2Me	H	**15f**	44
9	**10f** or **12f/11f**[d]	CH_2CO_2Me	H	**14f/15f**	52

[a] Refer to Table 2 for structures. [b] Except where noted, a single lactam stereoisomer was obtained, even when mixtures of oxaziridines were reacted (entries 5, 6, and 8). [c] Minor isomer from Table 2, entry 6; N-2 and C-3 configurations not determined. [d] This 2:1 mixture of oxaziridines was inseparable; a 2:1 ratio of lactams resulted from the photolysis of the mixture.

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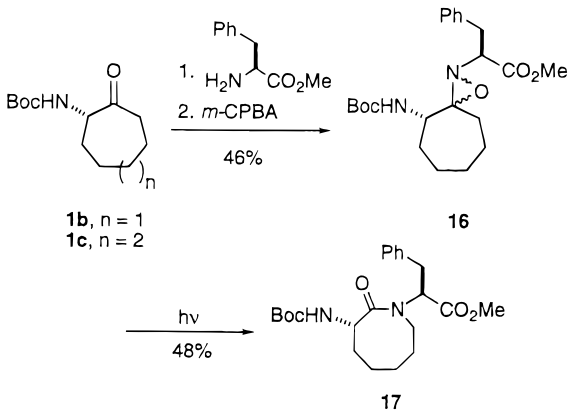
(17) The stereochemical assignment of these other oxaziridines (Table 2, entries 3−6) was not determined as rigorously as those derived from L- and D-phenylalanine methyl ester. The assignments were determined using the following information: (1) the predominance of one diastereomer, (2) the convergence of some to identical lactams, and (3) analogy with results from L-Phe-OMe.

Scheme 3



cally purified and photorearranged to a single diastereomeric lactam (Table 3, entry 8), the bulk of the oxaziridines could not be separated and gave a mixture of two diastereomeric lactams upon photorearrangement (Table 3, entry 9). Hence, the C-4 stereocenter was almost completely compromised during oxaziridine synthesis from this functionalized amino ester. It should be mentioned that glycine esters gave atypical (and, thus far, uninterpretable) results when oxaziridine syntheses from **1a** were attempted. However, the synthesis of the corresponding lactams of various ring sizes have been previously reported. Because of the absence of stereochemistry in glycine, such substituents can be easily incorporated into Freidinger lactams by coupling *N*-unsubstituted lactams with α-haloacetate esters (e.g., see Thorsett et al.[6d]).

Condensation of L-phenylalanine methyl ester and enantiopure cycloheptanone **1b** (Scheme 3) required larger amounts of tin catalyst to form the imines needed for the subsequent oxidation (almost a full equivalent was used). Even still, the oxaziridines **16** were isolated in only modest yield, although most of the remaining ketone **1b** could be recovered. The 2:1 ratio of diastereomeric oxaziridines converged onto a single lactam (**17**) upon photorearrangement. Therefore, the oxaziridines differ in N-2/C-3 stereochemistry, and the oxidant approach is less selective compared with the corresponding reaction using cyclohexanone **1a** (cf. Table 2, entry 1). Nevertheless, the formation of these oxaziridines and their photorearrangement to ζ-lactam **17** is significant because lactams of this size are difficult to obtain by other methods.[18] All attempts to form oxaziridines from cyclooctanone **1c** and L-phenylalanine methyl ester failed, even under forcing conditions (toluene reflux in the presence of tin catalyst).

Overall, photorearrangement of the dipeptidyl oxaziridines to Freidinger-type lactams proceeds in moderate to good yields, resulting in essentially one regioisomer (i.e., 3-substituted lactams). In many cases racemic ketone can be used, and subsequent separation of the resultant diastereomeric oxaziridines and photorearrangement provides stereodefined dipeptidyl lactams.

Conformational Analysis of Dipeptidyl Lactams 14a and 17. The conformation of ϵ-lactam **14a** was investigated by NMR and X-ray crystallography. ^{1}H-NMR decoupling experiments revealed that H-3 prefers the axial position in solution ($CDCl_3$), indicating that the

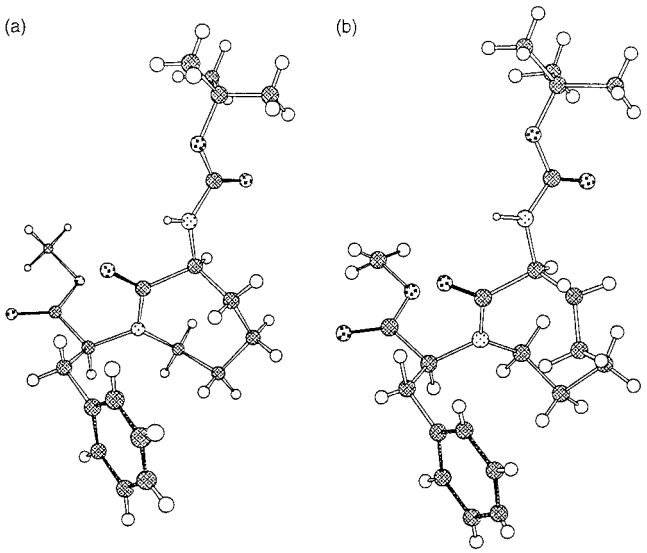
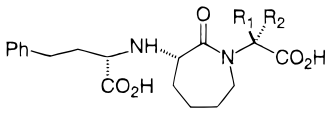


Figure 4. Ball-and-stick depictions of X-ray crystallographic structures of (a) **14a** and (b) **17**.



	R_1	R_2	IC_{50} (nM)[a]
18	H	H	19
19	Me	H	8
20	H	Me	57

[a] values for racemic lactams

Figure 5. Effect of Cα stereochemistry on ACE inhibition.

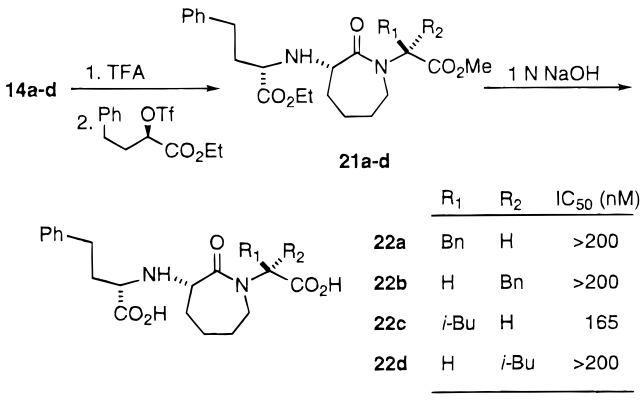
BocNH substituent is oriented equatorially and that the caprolactam is a well-behaved chairlike entity. Other coupling information gleaned from a COSY spectrum was consistent with this assumption. Unfortunately, 2-D NOESY experiments did not show any proximity between protons on the phenylalanine substructure and those of the lactam ring. Such information would have been useful in determining the preferred rotamer about the N-C_α bond (ϕ_2). However, an X-ray crystallographic study of **14a** revealed $\phi_2 = +61°$, $\phi_1 = +139°$, and $\psi_1 = -175°$ (Figure 4a). Similarly, crystallographic studies on ζ-lactam **17** confirmed a "lawn-chair" conformation for the eight-membered ring and indicated $\phi_2 = +63°$, $\phi_1 = +142°$, and $\psi_1 = -158°$ (Figure 4b). It is interesting that both molecules adopted such similar conformations with respect to the side chains.

Formation of Potential ACE Inhibitors. ACE is a proven target for the treatment of hypertension and congestive heart failure.[19] Like many clinically used ACE inhibitors (e.g., captopril and enalapril), Freidinger-type lactams such as **18** inhibit ACE well into the nanomolar range.[6b] As shown in Figure 5, the potency of derivatives bearing methyl substitution at C_α (**19** and **20**) depend on the configuration of that stereocenter.[6b] The original syntheses of compounds **18**−**20** led to mixtures of stereoisomers which were resolved to isolate the bioactive diastereomers in racemic form. Resolution of the eight-

(18) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 6857−6858.

(19) Kostis, J. B.; DeFelice, E. A. *Angiotensin-Converting Enzyme Inhibitors*; Alan R. Liss: New York, 1987.

Scheme 4



	R_1	R_2	IC_{50} (nM)
22a	Bn	H	>200
22b	H	Bn	>200
22c	*i*-Bu	H	165
22d	H	*i*-Bu	>200

membered lactam corresponding to **18** identified the *S*,*S* isomer as the better inhibitor (IC_{50} = 2 nM).[6b] The additional sterogenic center in **19** and **20** makes the task of stereoselective synthesis more challenging. To illustrate the utility of our chemistry toward the synthesis of new stereodefined Freidinger-type lactams of potential biological interest, we synthesized new C_α-substituted lactams (R = *i*-Bu or Bn). These particular substituents were chosen as prototypes to address the question of whether adding a hydrophobic group would increase potency by improving interaction with the S2′ binding site of the enzyme.

The synthesis of these compounds from lactams **14a**−**d** was accomplished according to the method of Attwood et al. as depicted in Scheme 4.[20] After deprotection of **14** with TFA, the 3-amino group was alkylated with the triflate derivative of ethyl *(R)*-2-hydroxy-4-phenylbutyrate to form **21** as a single diastereomer in 52−66% yield. Ester hydrolysis under basic conditions afforded the final compounds **22**.

These compounds were tested for their ability to inhibit purified ACE isolated from rabbit lung.[21] The IC_{50} value for **22c** was 165 nM, while those for compounds **22a**, **22b**, and **22d** were >200 nM. The benzyl-substituted compounds **22a** and **22b** were completely ineffective at the highest concentration tested (200 nM); isobutyl-substituted **22d** displayed 16% inhibition at this concentration (two experiments). It is clear that the additional steric bulk at the Cα adjacent to the ring nitrogen has a detrimental effect on inhibitory activity: compounds **22a**−**d** are all significantly less active than **18**−**20**, and the four-carbon isobutyl group is tolerated better than the seven-carbon benzyl group. This finding is consistent with a recent report for a series of closely related (mercaptoacetyl)-3-amino-ϵ-lactams.[6i] Whereas methyl substitution at Cα adjacent to the ring nitrogen with *S* stereochemistry was well-tolerated, benzyl or isopropyl substitution resulted in a 20- to 40-fold increase in the IC_{50} value. In addition, our finding that **22c** is more active than **22d** confirms the observation made with methyl-substituted compounds **19** and **20** that *S* stereochemistry at the Cα position is preferred over *R* stereochemistry for ACE binding.[6b]

(20) Attwood, M. R.; Hassall, C. H.; Kröhn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1011−1019.

(21) (a) Performed according to: Cushman, D. W.; Cheung, H. S. *Biochem. Pharmacol.* **1971**, *20*, 1637−1648. (b) ACE isolated from rabbit lung, substrate hippuryl-His-Leu, and captopril were obtained from Sigma (St. Louis, MO). Due to the insolubility of **8a**−**d** in water, ethanol was used as a cosolvent (final concentration 0.2%). The IC_{50} value for captopril was determined to be 38 nM without ethanol and 48 nM with 0.2% ethanol (lit. value[21a] = 23 nM).

Conclusions. The synthetic methodology described here is useful for obtaining seven- and eight-membered Freidinger lactams. Although the synthesis of the chiral spirocyclic oxaziridine intermediates often leads to the formation of more than one diastereomer, in many cases chromatographic separation provides a single diastereomer that can undergo photorearrangement to a stereodefined lactam. In some cases, the diastereomeric oxaziridines need not be separated since they converge upon the same lactam. A variety of substituents can be installed adjacent to the ring nitrogen by the simple expedient of using the appropriate α-amino ester in the oxaziridine formation.

Experimental Section

General Methods. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual solvent as an internal reference. Optical rotations were measured at ambient temperature; concentrations are reported in g/100 mL. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed in-house. Column chromatography was carried out with 230−400 mesh silica gel. Except where noted, all starting materials were purchased from Aldrich or Sigma Chemical Co. and used as received. The (*S*)-*tert*-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones (**1a**−**c**) were prepared as previously reported.[14]

General Procedure for the Synthesis of Oxaziridines. To a solution of ketone (1.0 equiv) in 5 mL of toluene (stored over 5 Å molecular sieves) was added 2.0 equiv of $NaHCO_3$, crushed 5 Å molecular sieves (250 mg/100 mg ketone), amino ester (4.2 equiv), and 20 mol % of Bu_2SnCl_2. The suspension was sealed under N_2, stirred for 3−20 h at room temperature, and then transferred via a wide-bore cannula to a −78 °C suspension of *m*-CPBA (1.5 equiv) in toluene. After 30 min the suspension was allowed to warm to ambient temperature, whereupon it was quenched with 10% aqueous $Na_2S_2O_3$ solution, diluted with Et_2O, and washed with saturated $NaHCO_3$ solution and saturated NaCl solution. After drying over Na_2SO_4 and concentration, the oil was chromatographed using flash silica gel and ethyl acetate/hexane mixtures ranging from 5:1 to 3:1 as eluent.

(2*R*,α*S*)-1′-(Phenylmethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (4a). According to the general procedure, cyclohexanone (0.500 g, 5.1 mmol) was allowed to react with L-phenylalanine methyl ester (3.76 g, 21 mmol), followed by *m*-CPBA (1.29 g, 7.58 mmol). Column chromatography with 40% ethyl acetate/hexane afforded the title compound as an oil (1.08 g, 79%): $[\alpha]_D = -54.7$ (*c* 1.1, $CHCl_3$); IR (neat) 2910, 2840, 1745, 1490 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (m, 1H), 1.08 (m, 1H), 1.39−1.67 (m, 8H), 3.12 (dd, *J* = 9.0, 16 Hz, 1H), 3.15 (dd, *J* = 5.1, 16 Hz, 1H), 3.53 (dd, *J* = 5.2, 9.0 Hz, 1H), 3.78 (s, 3H), 7.18−7.30 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.7, 24.4, 25.0, 27.5, 35.5, 37.2, 52.4, 65.6, 86.5, 127.1, 128.5, 129.4, 136.3, 170.0; MS (CI) *m*/*e* 276 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.08. Found: C, 69.78; H, 7.89; N, 5.00.

(2*R*,α*S*)-1′-(2-Methylpropyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid (4b) and (2*S*,α*S*) diastereomer (5b). According to the general procedure, cyclohexanone (1.0 g, 10.02 mmol) was allowed to react with L-leucine methyl ester (6.09 g, 42.8 mmol) followed by *m*-CPBA (2.63 g, 15.3 mmol). Column chromatography with 40% ethyl acetate/hexane afforded a major isomer (1.2 g, 50%, R_f = 0.60) and a minor isomer (0.15 g, 6%, R_f = 0.65), both as oils. Major isomer (**4b**): $[\alpha]_D = -38.7$ (*c* 3.6, $CHCl_3$); IR (neat) 2930, 2840, 1740, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.37−1.5 (m, 2H), 1.55−1.84 (m, 10H), 1.88−1.95 (m, 1H), 3.36 (dd, *J* = 4.5, 9.5 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1, 23.3, 24.0, 24.8, 25.2, 25.2, 27.9, 36.1, 39.2, 52.2, 63.6, 85.8, 171.8; MS (CI) *m*/*e* 242 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found: C, 64.31; H, 9.89, N, 6.10. Minor isomer (**5b**): IR

(neat) 2920, 2840, 1745, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 6.3$ Hz, 3H), 1.25−2.01 (m, 13H), 3.35 (t, $J = 6.0$ Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.4, 23.2, 24.4, 25.0, 25.1, 25.6, 28.5, 36.3, 42.5, 52.3, 64.0, 85.0, 171.7; MS (EI) m/e 242 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found: C, 64.40; H, 10.00; N, 5.98.

(2*R*,α*S*)-1′-(1-Methylethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (4c). According to the general procedure, cyclohexanone (0.250 g, 2.5 mmol) was allowed to react with L-valine methyl ester (1.37 g, 10.5 mmol), followed by *m*-CPBA (0.64 g, 3.75 mmol). Column chromatography with 40% ethyl acetate/hexane afforded the title compound (0.466 g, 82%) as an oil: $[\alpha]_D = -63.5$ (*c* 2.2, $CHCl_3$); IR (neat) 2920, 2840, 1745, 1660, 1430 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, $J = 9.9$ Hz, 3H), 1.01 (d, $J = 9.9$ Hz, 3H), 1.39 (m, 2H), 1.58−1.85 (m, 8H), 2.22 (m, 1H), 3.13 (d, $J = 7.6$ Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 19.5, 23.8, 24.5, 25.1, 28.6, 30.6, 35.6, 51.9, 69.5, 86.7, 170.8; MS (CI) m/e 228 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.15. Found: C, 63.28; H, 9.50; N, 6.08.

1′-[1-Oxa-2-azaspiro[2.5]oct-2-yl]butanedioic Acid Dimethyl Ester (4d/5d). According to the general procedure, cyclohexanone (0.500 g, 5.1 mmol), was allowed to react with L-aspartic acid dimethyl ester (0.850 g, 10 mmol) followed by *m*-CPBA (1.29 g, 7.5 mmol). Column chromatography with 40% ethyl acetate/hexane afforded a less polar isomer 1 ($R_f =$ 0.70, 0.687 g, 52%) and a more polar isomer 2 ($R_f = 0.44$, 0.597 g, 45%). Isomer 1: $[\alpha]_D = -33.2$ (*c* 0.7, $CHCl_3$); IR (neat) 2935, 2800, 1745, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29−2.01 (m, 10H), 2.87 (dd, $J = 4.9$, 16.4 Hz, 1H), 3.04 (dd, $J =$ 7.3, 16.4 Hz, 1H), 3.72 (s, 3H) 3.78 (s, 3H), 3.76−3.80 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.3, 24.7, 25.5, 28.5, 36.2, 36.5, 52.4, 53.0, 61.2, 87.2, 169.4, 171.5; MS (EI) m/e 258 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.01; H, 7.44; N, 5.44. Found: C, 56.07; H, 7.80; N, 5.28. Isomer 2: $[\alpha]_D = -24.1$ (*c* 1.0, $CHCl_3$); IR (neat) 2940, 2835, 1740, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29−1.88 (m, 10H), 2.69 (dd, $J = 5.4$, 16.4 Hz, 1H), 2.99 (dd, $J = 8.0$, 16.4 Hz, 1H), 3.71 (s, 3H), 3.73 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.1, 25.4, 25.5, 28.3, 35.2, 36.1, 52.6, 53.1, 60.9, 86.3, 170.4, 170.7; MS (CI) m/e 258 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.19; N, 5.09.

1′-[(Benzyloxy)methyl]-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (4e/5e). According to the general procedure, cyclohexanone (0.100 g, 1.02 mmol) was allowed to react with *O*-benzyl-L-serine methyl ester (0.84 g, 4.42 mmol) followed by *m*-CPBA (0.263 g, 1.53 mmol). Column chromatography with 25% ethyl acetate/hexane provided the less polar isomer 1 ($R_f = 0.60$, 0.083 g, 27%) and the more polar isomer 2 ($R_f = 0.48$, 0.124 g, 40%) as yellow oils. Isomer 1: IR (neat) 2910, 2850, 1740, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25−1.85 (m, 10H), 3.48 (t, $J = 4.5$ Hz, 1H), 3.76 (s, 3H), 3.89 (m, 2H), 4.65 (AB q, $J = 12.3$ Hz, Dn = 42.6 Hz, 2H), 7.26−7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 24.5, 25.1, 27.8, 35.8, 52.2, 65.4, 69.7, 73.5, 85.5, 127.6, 127.7, 128.3, 137.7, 168.9; MS (CI) m/e 306 ($M^+ + 1$), HRMS calcd for ($M^+ + 1$) $C_{17}H_{24}NO_4$: 306.1705, found 306.1715. Isomer 2: $[\alpha]_D$ −22.9 (*c* 0.9, $CHCl_3$), IR (neat) 2920, 2840, 1740, 1445 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25−1.89 (m, 10H), 3.65 (dd, $J = 4.8$, 7.4 Hz, 1H), 3.79 (s, 3H), 3.81−3.83 (m, 2H), 4.53 (s, 2H), 7.29−7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 24.1, 24.9, 28.2, 35.6, 52.3, 64.3, 68.3, 73.3, 86.1, 127.5, 127.6, 128.1, 137.1, 169.3; MS (CI) m/e 306 ($M^+ + 1$); HRMS calcd for ($M^+ + 1$) $C_{17}H_{24}NO_4$: 306.1705, found: 306.1688.

(2*S*,3*S*,4*S*,α*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (10a). According to the general procedure, **1a** (0.250 g, 1.15 mmol) was allowed to react with L-phenylalanine methyl ester (0.800 g, 4.92 mmol), followed by *m*-CPBA (0.290 g, 1.71 mmol). Column chromatography with 25% ethyl acetate/hexane provided the title compound (0.180 g, 72%): $[\alpha]_D = -50.8$ (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3420, 3000, 2950, 1790, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01−1.21 (m, 2H), 1.44 (s, 9H), 1.45−2.39 (m, 6H), 3.05 (dd, $J = 6.8$, 13.6 Hz, 1H), 3.26 (dd, $J = 7.3$, 13.2 Hz, 1H), 3.56 (t, $J = 7.10$ Hz, 1H), 3.70 (s, 3H), 3.73 (m, 1H), 5.00 (brs, 1H), 7.17−7.34 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 23.4, 23.7, 27.4, 28.3, 32.1, 37.4, 52.3, 65.6, 79.2, 85.3, 127.2, 128.7, 129.2, 135.7, 156.3, 170.2; MS (EI) m/e 391 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.30; H, 8.00; N, 6.78.

(2*R*,3*R*,4*S*,α*R*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (12b). According to the general procedure, **1a** (0.906 g, 4.25 mmol) was allowed to react with D-phenylalanine methyl ester (3.18 g, 17.8 mmol) followed by *m*-CPBA (1.08 g, 6.37 mmol). Column chromatography with 25% ethyl acetate/hexane provided **12b** (0.940 g, 57%): $[\alpha]_D = -44.8$ (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3415, 3000, 2990, 2940, 1795, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.42 (app td, $J =$ 12.8, 3.7, 1H), 1.20−1.46 (m, 4H), 1.50 (s, 9H), 1.69 (m, 2H), 2.01 (m, 1H), 3.01−3.19 (m, 2H), 3.50 (dd, $J = 4.6$, 9.2 Hz, 1H), 3.6 (m, 1H), 3.81 (s, 3H), 4.63 (d, $J = 8.4$ Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.4, 24.5, 27.5, 28.8, 31.8, 37.3, 51.1, 52.5, 65.9, 77.3, 85.8, 127.5, 127.6, 129.0, 130.0, 156.4, 171.1; MS (EI) m/e 391 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.30; H, 7.89; N, 7.30. Another isomer (**13b**) was also isolated in 4% yield with spectra identical to **10a** (i.e., **13b** is the antipode of **10a**).

(2*S*,3*S*,4*S*,α*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-(2-methylpropyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (10c) and Isomer 11c. According to the general procedure, **1a** (0.602 g, 2.8 mmol) was allowed to react with L-leucine methyl ester (1.69 g, 11.76 mmol), followed by *m*-CPBA (0.722 g, 4.2 mmol). Column chromatography with 1:5 ethyl acetate/hexane provided **10c** (0.475 g, 49%) as an oil: $[\alpha]_D = -22.1$ (*c* 1.7, $CHCl_3$); IR (neat) 3450, 2920, 2840, 1740, 1700, 1600 cm^1; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, $J = 4.2$ Hz, 3H), 0.95 (d, $J = 4.2$ Hz, 3H), 1.12−2.30 (m, 11H), 1.42 (s, 9H), 3.37 (dd, $J = 3.6$, 10.5 Hz, 1H), 3.72 (br d, 1H), 3.79 (s, 3H), 5.07 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.3, 23.8, 24.2, 24.9, 25.8, 27.9, 28.8, 33.1, 39.9, 52.6, 52.7, 63.5, 79.6, 85.2, 156.0, 171.6; MS (EI) m/e 357 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.64, H; 8.97; N, 7.86. Found: C, 60.30; H, 9.18; N, 7.48. The minor isomer **11c** was also isolated (0.142 g, 14%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (br d, 6H), 1.28−2.15 (m, 11H), 1.44 (s, 9H), 3.35 (dd, $J = 5.0$, 9.1 Hz, 1H), 3.78 (m, 4H), 4.59 (br d, $J =$ 7.2 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.2, 23.1, 24.2, 24.4, 25.1, 27.6, 28.3, 31.1, 38.7, 51.6, 52.1, 63.3, 79.0, 84.8, 156.2, 171.5.

(2*SR*,3*SR*,4*S*,αR)-4-[[(1,1-Dimethylethoxy)carbonyl]-amino]-α-(2-methylpropyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (10d/12d). According to the general procedure, **1a** (1.0 g, 4.6 mmol) was allowed to react with D-leucine methyl ester (2.75 g, 19.3 mmol) followed by *m*-CPBA (1.20 g, 6.9 mmol). Column chromatography with 40% ethyl acetate/hexane afforded the title compound as a mixture of diastereomers as determined by ^1H-NMR integration (ca. 1:1 ratio of isomers, 1.02 g, 60%). Isomer 1: For analytical purposes, a pure sample of this isomer could be obtained by careful chromatography. IR (neat) 3451, 2910, 2820, 2840, 1740, 1700, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.0$ Hz, 3H), 1.21−2.23 (m, 11H), 1.44 (s, 9H), 3.36 (m, 1H), 3.73 (s, 3H), 3.80 (m, 1H), 4.60 (d, 3.6 Hz, 1H): ^{13}C NMR (74.5 Hz, $CDCl_3$) δ 22.0, 22.8, 23.9, 24.3, 24.6, 25.1, 27.8, 28.2, 31.2, 51.2, 52.0, 63.1, 78.8, 84.7, 155.9, 171.5. Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.64; H, 8.97; N, 7.86. Found: C, 60.29; H, 8.70; N, 7.48. Isomer 2: ^1H NMR (diagnostic peaks only, 300 MHz, $CDCl_3$) δ 0.90 (d, $J =$ 6.6 Hz, 3H), 0.94 (d, $J = 6.3$ Hz, 3H), 1.42 (s, 9H), 3.78 (s, 3H): ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.2, 23.1, 24.2, 24.3, 24.5, 25.3, 27.8, 31.0, 51.5, 52.2, 63.2, 78.8, 84.1, 156.0, 170.3; MS (CI) m/e 357 ($M^+ + 1$).

(2*S*,3*S*,4*S*,α*S*)-4-[[(1,1-dimethylethoxy)carbonyl)amino]-α-(1-methylethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (10e), the (2*S*,3*S*,4*R*,α*S*) diastereomer 11e, and the (2*R*,3*R*,4*S*,α*S*) Diastereomer 12e. According to the general procedure, **1a** (0.500 g, 2.3 mmol) was allowed to react with L-valine methyl ester (1.26 g, 9.6 mmol) followed

by *m*-CPBA (0.593 g, 3.4 mmol). Column chromatography with 40% ethyl acetate/hexane afforded a less polar isomer **11e** (R_f = 0.65, 0.208 g, 26%) and a more polar, inseparable mixture of isomers **10e** and **12e** (R_f = 0.53, 0.312 g, 40%, ratio of isomers **10e**:**12e** ca. 4−5:1) as oils. **11e**: $[\alpha]_D$ = −12.0 (*c* 2.5, $CDCl_3$); IR (neat) 3390, 2910, 2840, 1730, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J* = 9.0 Hz, 3H), 0.99 (d, *J* = 9.1 Hz, 3H), 1.20−2.30 (m, 9H), 3.12 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.82−3.87 (m, 1H), 4.62 (br d, *J* = 9.0 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 19.1, 19.4, 19.6, 24.4, 24.6, 24.7, 31.1, 31.5, 51.6, 52.3, 69.7, 79.4, 86.3, 156.7, 171.2; MS (EI) *m*/*e* 343 (M^+ + 1). Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.62; H, 8.83; N, 8.18. Found: C, 59.96; H, 9.20; N,7.80. **10e**: IR (neat) 3410, 3000, 2900, 1740, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J* = 13.8 Hz, 3H), 1.12−2.30 (m, 9H), 1.43 (s, 9H), 1.70 (d, *J* = 14.1 Hz, 3H), 3.17 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.81 (m, 1H), 5.09 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 19.5, 19.7, 24.8, 28.8 (2C), 31.1, 31.6, 51.9, 52.2, 69.2, 79.2, 85.1, 155.6, 169.7; MS (CI) *m*/*e* 343 (M^+ + 1). Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.62; H, 8.83; N, 8.18. Found: C, 60.00, H, 8.83; N, 8.23. **12e** (diagnostic peaks only): ^1H NMR (300 MHz, $CDCl_3$): δ 3.14 (d, *J* = 5.1 Hz, 1 H), 3.72 (s, 3 H); ^{13}C NMR (74.5Hz, $CDCl_3$) δ 18.7, 24.2, 27.7, 50.2, 70.3.

(2*S*,3*S*,4*S*,α*S*)-4-[[(1,1-Dimethylethoxy]carbonyl]amino]-1-oxa-2-azaspiro[2.5]oct-2-yl]-butanedioic acid dimethyl ester (10f), the (2*R*,3*R*,4*S*,α*S*) Diastereomer (12f), and a (4*R*,α*S*) Diastereomer (11f or 13f). According to the general procedure, **1a** (0.500 g, 2.3 mmol) was allowed to react with L-aspartic acid dimethyl ester (1.55 g, 9.6 mmol) followed by *m*-CPBA (0.593 g, 3.4 mmol). Column chromatography with 40% ethyl acetate/hexane afforded a less polar, inseparable mixture of **10f** and 40% ethyl acetate/hexane (R_f = 0.41, 0.471 g, 55%, isomer 1:2 ca. 2−3:1) and a more polar isomer 3 (R_f = 0.25, 0.083 g, 9%) as oils. **10f** and **12f**: IR (neat) 3460, 3440, 2940, 2820, 1740, 1720 cm^{-1}; MS (EI) *m*/*e* 373 (M^+ + 1) HRMS calcd for (M^+ + 1) $C_{17}H_{28}N_2O_7$: 373.1915, found 373.1967. **10f**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−2.14 (m, 8H), 1.42 (s, 9H), 2.74−3.12 (m, 2H), 3.67−3.86 (m, 2H), 3.71 (s, 3H), 3.78 (s, 3H), 4.49 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$, diagnostic peaks only) δ 23.4, 24.0, 28.3, 32.0, 36.2, 52.1, 52.6, 60.1, 155.7, 169.0, 170.9. **12f** (diagnostic peaks only): ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.76 (s, 3H), 4.52 (br d, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 23.9, 24.3, 31.3, 35.9, 60.6, 156.0, 168.2, 171.1. **11f** or **13f**: IR (neat) 3440, 3330, 2930, 2440, 1740, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20−2.20 (m, 8H), 1.42 (s, 9H), 2.70 (dd, *J* = 5.1, 16.7 Hz, 1H), 3.70 (dd, *J* = 8.3, 16.6 Hz, 1H), 3.68−3.72 (m, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 4.89 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 23.2, 24.1, 27.1, 28.1, 32.1, 35.1, 51.9, 52.0, 52.5, 59.7, 79.0, 84.6, 155.6, 169.4, 169.8; MS (EI) *m*/*e* 373 (M^+ + 1) HRMS calcd for (M^+ + 1) $C_{17}H_{29}N_2O_7$: 373.1975, found: 373.1970.

[2*S*,3*S*,5*R*,α*S*]-5-Methyl-α-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (6) and Isomer. (*R*)-3-Methylcyclohexanone (1.10 g, 9.8 mmol) was allowed to react with L-phenylalanine methyl ester (2.52 g, 14 mmol) followed by *m*-CPBA (2.52 g, 14 mmol). Column chromatography with 40% ethyl acetate/hexane afforded the title compound (R_f = 0.44 (20% ethyl acetate/hexane), 2.44 g, 86%) as an oil: $[\alpha]_D$ = −49.2 (*c* 2.8, $CDCl_3$); IR (neat) 2956, 1739, 1600, 1560 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6 Hz, 3H), 1.10 (m, 2H), 1.51 (m, 7H), 3.10 (dd, *J* = 6.9, 13.5 Hz, 1H), 3.21 (dd, *J* = 6.9, 13.5 Hz, 1H), 3.51 (apparent t, *J* = 6.9 Hz, 1H), 3.72 (s, 3H), 7.12−7.30 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.7, 22.8, 27.4, 31.1, 33.2, 37.8, 43.9, 52.7, 67.0, 86.8, 127.5, 129.1, 129.7, 136.5, 171.1; MS (EI) *m*/*e* 290 (M^+ + 1); HRMS calcd for $C_{17}H_{24}NO_3$: 290.1756, found 290.1761. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.83. Found: C, 70.20, H, 8.38; N, 4.61. A minor isomer was also isolated (R_f = 0.56 (20% ethyl acetate/hexane), 0.34 g, 12%) as an oil: IR (neat) 2950, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.2 Hz, 3H), 1.00 (m, 1H), 1.48−1.87 (m, 8H), 3.25 (m, 2H), 3.47 (t, *J* = 6.6 Hz, 1H), 3.63 (s, 3H), 7.22−7.31 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.9, 23.3, 31.2, 33.5, 35.6, 35.8, 39.0, 51.8, 67.7, 85.5, 126.7, 128.3, 129.3, 136.6, 170.0; MS (EI) *m*/*e* 290 (M^+ + 1).

[2*R*,3*S*,5*R*,α*R*]-5-Methyl-α-(phenylmethyl)-1-oxa-2-azaspiro[2.5]octane-2-acetic Acid Methyl Ester (8) and Isomer. (*R*)-3-Methylcyclohexanone (1.1 g, 10 mmol) was allowed to react with D-phenylalanine methyl ester (2.52 g, 14 mmol). Column chromatography with 40% ethyl acetate/hexane afforded the title compound (R_f = 0.60 (20% ethyl acetate/hexane), 2.62 g, 93%) as an oil: $[\alpha]_D$ = +83.1 (*c* 2.4, $CDCl_3$); IR (neat) 3100, 2940, 1700, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 3H), 1.02 (m, 1H), 1.18−1.81 (m, 8H), 3.09 (dd, *J* = 7.3, 13.6 Hz, 1H), 3.21 (dd, *J* = 13.6, 6.5), 3.50 (t, *J* = 7.10 Hz, 1H), 3.73 (s, 3H), 7.12−7.30 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.9, 22.7, 30.9, 33.3, 35.5, 35.9, 37.9, 52.6, 66.8, 86.8, 127.5, 129.0, 129.7, 136.6, 171.1; MS (EI) *m*/*e* 290 (M^+ + 1); HRMS calcd for $C_{17}H_{24}NO_3$: 290.1756, found 290.1763. A **minor isomer** was obtained as an oil (R_f = 0.68 (20% ethyl acetate/hexane), 0.260 g, "9%", neither purified nor fully characterized): ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.5 Hz, 3H), 1.00 (m, 1H), 1.22−1.90 (m, 8H), 3.25 (apparent d, 2H), 3.46 (t, *J* = 6.8 Hz, 3H), 3.65 (s, 3H), 7.22−7.32 (m, 5H).

(2*S*R*,3*S*R*,4*S*,α*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]-amino]-α-(phenylmethyl)-1-oxa-2-azaspiro[2.5]nonane-2-acetic Acid (16). According to the general procedure, ketone **1b** (0.262 g, 0.65 mmol) was reacted with L-phenylalanine methyl ester (0.800 g, 2.60 mmol) with dibutyltin dichloride (173 mg, 0.57 mmol, 87 mol %), followed by *m*-CPBA (0.262 g, 0.65 mmol). Column chromatography with 40% ethyl acetate/hexane afforded **16**, as an inseparable mixture of diastereomers (major:minor 1.8:1, 0.120 g, 46%). Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.00−1.41 (m, 2H), 1.42 (s, 9H), 1.43−2.10 (m, 8H), 3.04 (dd, *J* = 6.9, 13.5 Hz, 1H), 3.22 (m, 1H), 3.56 (t, *J* = 6.9 Hz, 1H), 3.71 (s, 3H), 3.81 (m, 1H), 5.15 (d, *J* = 3.9 Hz, 1H), 7.15−7.40 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.6, 23.4, 26.7, 28.3, 29.7, 32.1, 37.1, 52.3, 53.6, 65.4, 79.1, 86.1, 128.1, 129.3, 129.6, 135.6, 158.2, 170.4; MS (CI) *m*/*e* 405 (M^+ + 1). Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found: C, 65.03; H, 8.30; N, 6.80. Minor isomer (diagnostic peaks only): ^1H NMR (300 MHz, $CDCl_3$) δ 3.30 (dd, *J* = 6.9, 13.5 Hz, 1H), 3.15 (dd, *J* = 6.3, 15.6 Hz, 1H), 3.49 (t, *J* = 6.6 Hz, 1H), 3.64 (s, 3H), 4.90 (d, *J* = 6.0 Hz, 1H).

General Procedure for Lactam Synthesis. The oxaziridine was dissolved in benzene (0.05−0.10 M) and placed in a quartz photolysis tube. The solution was degassed by bubbling nitrogen through it for 45 min and then photolyzed in a Rayonet (merry-go-round) chamber at 254 nm for 2−4 h.

(3*S*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (14a). Oxaziridine **10a** (0.260 g, 0.66 mmol) was photolyzed for 4 h. Concentration followed by column chromatography with 40% ethyl acetate/hexane yielded **14a** as a white solid (0.187 g, 72%): mp 108 °C; $[\alpha]_D$ = −57.0 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3400, 3000, 2900, 1740, 1700, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (m, 1H), 1.42 (s, 9H), 1.5−1.9 (m, 5H), 3.08 (dd, *J* = 9.8, 14 .2 Hz, 1H), 3.31 (m, 3H), 3.72 (s, 3H), 4.20 (dd, *J* = 5.8, 10.3 Hz, 1H), 5.14 (dd, *J* = 6.3, 9.8 Hz, 1H), 5.89 (d, *J* = 5.5 Hz, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 26.9, 27.7, 28.4, 32.2, 35.1, 47.3, 52.2, 53.6, 61.0, 79.3, 126.9, 128.6, 129.1, 137.0, 155.1, 171.1, 173.4; MS (EI) *m*/*e* 390 (M^+ + 1). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.80; H, 7.69; N, 7.50.

(3*S*,α*R*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-Acetic Acid Methyl Ester (14b). Oxaziridine **12b** (0.269 g, 0.68 mmol) was photolyzed for 3 h. Column chromatography with 40% ethyl acetate/hexane yielded **14b** (0.182 g, 68%): $[\alpha]_D$ = +48.3 (*c* 0.20, $CDCl_3$); IR ($CHCl_3$) 3400, 3000, 2900, 1745, 1700, 1645 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.27−1.41 (m, 2H), 1.47 (s, 9H), 1.52−1.90 (m, 4H), 2.92 (dd, *J* = 4.0, 15.3 Hz, 1H), 3.20 (m, 2 H), 3.43 (dd, *J* = 5.0, 14.4 Hz, 1H), 3.75 (s, 3H), 4.34 (dd, *J* = 6.2, 9.8 Hz, 1H), 4.83 (dd, *J* = 4.9, 10.5 Hz, 1H), 6.00 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 26.7, 27.7, 28.2, 35.0, 40.0, 48.8, 52.2, 53.4, 62.1, 79.1, 126.6, 128.4, 128.7, 137.2, 155.0, 170.6, 173.2; MS (EI) *m*/*e* 391 (M^+ + 1). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.63; H, 8.00; N, 7.22.

(3*S*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(2-methylpropyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (14c). Oxaziridine **10c** (0.400 g, 1.12 mmol) was photolyzed for 4 h. Column chromatography with 15% ethyl acetate/hexane afforded **14c** as a white solid (0.244 g, 61%): mp 122 °C; $[\alpha]_D = -42.0$ (*c* 0.3, $CHCl_3$), IR (KBr) 3390, 2980, 2940, 2900, 1740, 1795, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.3 HZ, 3H), 0.91 (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.45−2.10 (m, 9H), 3.36 (m, 2H), 3.71 (s, 3H), 4.34 (m, 1H), 5.37 (dd, J = 6.0, 9.6 Hz, 1H), 6.00 (br d, J = 6.0 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.7, 23.1, 24.9, 27.8, 27.9, 28.3, 32.6, 37.9, 46.1, 52.3, 53.7, 56.4, 79.2, 155.1, 171.9, 173.8; MS (EI) *m*/*e* 356 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.64; H, 9.05; N, 7.85. Found: C, 60.39; H, 9.45; N, 7.60.

(3*S*,α*R*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(2-methylpropyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (14d). A 1:1 mixture of oxaziridine diastereomers **10d** and **12d** (0.30 g, 0.84 mmol) was photolyzed for 3 h. Column chromatography with 40% ethyl acetate/hexane afforded a single lactam **14d** (0.177 g, 59%): $[\alpha]_D = +41.5$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$) 3400, 2930, 1740, 1730, 1700, 1640 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6, Hz, 3H), 1.22−2.10 (m, 9H), 1.43 (s, 9H), 3.23 (dd, J = 4.8, 15.3 Hz, 1H), 3.46 (dd, J = 11.7, 15.6 Hz, 1H), 3.69 (s, 3H), 4.41 (dd, J = 6.0, 9.6 Hz, 1H), 5.21 (dd, J = 4.5, 9.9 Hz, 1H), 6.10 (d, J = 5.7 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.8, 23.1, 24.9, 27.8, 28.3, 29.6, 32.6, 37.9, 46.0, 52.2, 53.7, 56.4, 79.2, 155.0, 171.8, 173.8; MS (EI) *m*/*e* 356 ($M^+ + 1$). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.64; H, 9.05; N, 7.85. Found: C, 60.59; H, 8.71; N, 7.68.

(3*S*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(1-methylethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (14e). A mixture of oxaziridine diastereomers **10e** and **12e** (ca. 4−5:1, 0.200 g, 0.58 mmol) was photolyzed for 4 h. Column chromatography with 40% ethyl acetate/hexane afforded **14e** (0.110 g, 59%) as a single isomer: $[\alpha]_D = -99.8$ (*c* 0.7, $CDCl_3$); IR ($CHCl_3$) 3420, 3000, 2900, 1740, 1700, 1640 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (dd, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.22−2.21 (m, 7H), 1.43 (s, 9H), 3.35 (dd, J = 11.4, 15.9 Hz, 1H), 3.58 (dd, J = 5.4, 15.6 Hz, 1H), 3.69 (s, 3H), 4.37 (dd, J = 4.2, 4.8 Hz, 1H), 4.69 (d, J = 9.9 Hz, 1H), 6.01 (d, J = 5.4 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 20.0, 20.2, 27.9, 28.4, 28.5, 28.8, 33.0, 46.7, 52.3, 54.2, 64.4, 79.7, 155.5, 171.3, 174.3; MS (CI) *m*/*e* 343 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.62; H, 8.83; N, 8.18. Found: C, 59.74; H, 9.22; N, 7.98.

(3*R*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(1-methylethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (15e). Oxaziridine **11e** (0.220 g, 0.64 mmol) was photolyzed for 4 h. Column chromatography with 40% ethyl acetate/hexane afforded **15e** (0.130 g, 59%) along with an unseparable isomer (ca.7−8:1). **15e**: IR ($CHCl_3$) 3400, 3000, 2900, 1790, 1695, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.22−2.21 (m, 7H), 1.44 (s, 9H), 3.29 (dd, J = 11.4, 15.3 Hz, 1H), 3.53 (dd, J = 5.1, 14.7 Hz, 1H), 3.72 (s, 3H), 4.37 (m, 1H), 4.94 (d, J = 8.0 Hz, 1H), 6.01 (d, J = 5.7 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 18.6, 19.5, 23.3, 27.4, 28.3, 28.4, 32.5, 43.5, 52.0, 53.5, 61.5, 79.4, 155.1, 171.3, 173.7. Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.62; H, 8.83; N, 8.18. Found: C, 60.00; H, 8.89; N, 8.14. Minor isomer (diagnostic peaks only): ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 3.76 (s, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 23.8, 27.6; MS (CI) *m*/*e* 373 ($M^+ + 1$).

(3*R*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(1-methylethyl)-2-oxo-1*H*-azepin-1-yl]-butanedioic Acid Dimethyl Ester (15f). Oxaziridine **10f** or **12f** (0.050 g, 13 mmol) was photolyzed for 4 h. Column chromatography with 40% ethyl acetate/hexane afforded **15f** (0.022 g, 44%): $[\alpha]_D = -30.6$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3400, 3000, 1740, 1690, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.51−2.00 (m, 6H), 2.75 (dd, J = 7.4, 16.6 Hz, 1H), 3.13 (dd, J = 6.5, 16.6 Hz, 1H), 3.31 (dd, J = 3.3, 15.2 Hz, 1H), 3.57 (dd, J = 11.3, 15.2 Hz, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 4.32 (dd, J = 6.1, 9.6 Hz, 1H), 5.00 (t, J = 7.1 Hz, 1H), 5.89 (d, J = 5.50 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 27.6, 27.7, 28.3, 32.3, 34.5, 49.1, 52.0, 52.6, 53.7, 58.0, 79.4, 155.1, 170.2, 171.3, 173.4; MS (CI) *m*/*e* 373 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{28}N_2O_7$: C, 54.82; H, 7.57; N, 7.52. Found: C, 54.80; H, 7.63, H, 7.96; N, 7.10.

(3*SR*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-α-(1-methylethyl)-2-oxo-1*H*-azepin-1-yl]-butanedioic Acid Dimethyl Ester (14f/15f). A mixture of two diastereomeric oxaziridines (**11f** and either **10f** or **12f**, ca. 2:1, 0.200 g 0.53 mmol) was photolyzed for 4 h. Column chromatography with 40% ethyl acetate/hexane afforded a mixture of distereomers **14f** and **15f** (ca. 2:1 ratio, 0.104 g, 52%) which were difficult to separate by chromatography. **14f**: IR ($CHCl_3$) 3400, 3000, 1730, 1700, 1650 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.53−2.00 (m, 6H), 2.88 (dd, J = 8.5, 17.1 Hz, 1H), 3.20 (dd, J = 5.2, 17.1 Hz, 1H), 3.36 (m, 1H), 3.57 (dd, J = 7.8, 15.6 Hz, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 4.35 (m, 1H), 4.71 (dd, J = 5.3, 8.4 Hz, 1H), 5.88 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 26.6, 27.7, 28.4, 32.2, 34.7, 50.4, 52.1, 52.6, 53.3, 59.3, 79.4, 155.0, 169.9, 171.5, 173.3. Anal. Calcd for $C_{17}H_{28}N_2O_7$: C, 54.82; H, 7.57; N, 7.52. Found: C, 54.80; H, 7.96; N, 7.10. Peaks for the minor isomer in the ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (74.5 MHz, $CDCl_3$) matched spectra for **15f** above.

(3*R*,α*S*)-Hexahydro-4-methyl-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (7). Oxaziridine **6** (0.400 g, 1.3 mmol) was photolyzed in benzene for 2 h. Column chromatography with 40% ethyl acetate/hexane afforded **7** (0.350 g, 88%): $[\alpha]_D = -80.9$ (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) 2930, 2910, 1730, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 1.19−1.30 (m, 2H), 1.57−1.82 (m, 4H), 2.20 (dd, J = 9.5, 13.6 Hz, 1H), 2.40 (br d, J = 13.6 Hz, 1H), 3.06 (dd, J = 10.3, 14.3 Hz, 1H), 3.21 (m, 1H), 3.33 (dd, J = 5.8, 14.5 Hz, 1H), 3.71 (s, 3H), 5.25 (dd, J = 5.8, 10.3 Hz, 1H), 7.12−7.35 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 21.9, 26.4, 28.7, 35.2, 37.9, 44.4, 47.6, 52.1, 59.7, 126.6, 128.4, 129.0, 137.2, 171.6, 174.7; MS (EI) *m*/*e* 290 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.83. Found: C, 70.41; H, 8.38; N, 4.68.

(6*R*,α*R*)-Hexahydro-4-methyl-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (9). Oxaziridine **8** (0.600 g, 2.07 mmol) was photolyzed in benzene for 2 h. Column chromatography with 40% ethyl acetate/hexane afforded **9** (0.495 g, 82%) as a white solid: mp 107 °C. $[\alpha]_D = -83.1$ (*c* 2.4, $CHCl_3$), IR (KBr) 3100, 2900, 2820, 1735, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.9 Hz, 3H), 1.11−1.81 (m, 6H), 2.30 (dd, J = 1.5, 13.8 Hz, 1H), 2.43 (m, 1H), 3.10 (m, 2H), 3.29 (dd, J = 6.0, 14.1 Hz, 1H), 3.70 (s, 3H), 5.13 (dd, J = 6.3, 9.9 Hz, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 20.9, 23.0, 33.7, 35.7, 37.4, 38.7, 52.4, 54.8, 60.7, 127.0, 128.8, 129.5, 137.7, 172.0, 176.1; MS (EI) *m*/*e* 290 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.83. Found: C, 70.42; H, 8.18; N, 4.71.

(3*S*,α*S*)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-hexahydro-2-oxo-α-(phenylmethyl)-1(2*H*)-azocine-acetic Acid Methyl Ester (17). Oxaziridine **16** (0.100 g, 0.24 mmol) was photolyzed for 4 h. Concentration followed by column chromatography with 40% ethyl acetate/hexane afforded **17** as a white solid (0.048 g, 48%): mp 118 °C; $[\alpha]_D = -76.2$ (*c* 0.3, $CHCl_3$); IR (KBr) 3380, 2985, 2970, 2930, 1735, 1700, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40−1.79 (m, 6H), 1.43 (s, 9H), 1.99 (m, 1H), 3.04 (dd, J = 8.1, 14.1 Hz, 1H), 3.38 (m, 3H), 3.68 (s, 3H), 3.72 (m, 1H), 4.60 (m, 1H), 5.10 (t, J = 7.8 Hz, 1H), 5.54 (d, J = 7.6 Hz, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 23.3, 24.6, 28.3, 29.7, 34.9, 36.7, 45.0, 50.3, 52.1, 59.2, 79.3, 126.7, 128.4, 129.0, 137.0, 154.9, 171.2, 173.5; MS (CI) *m*/*e* 405 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found: C, 65.28; H, 8.18; N, 6.68.

General Procedure for N-Deprotection and Side Chain Installation. (3*S*,α*S*)-3-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]amino]-hexahydro-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (21a). According to the literature procedure,[20] to a solution of lactam **14a** (0.260 g, 0.67 mmol) in 10 mL of CH_2Cl_2 was added 5 mL of TFA dropwise. After stirring at room temperature for 2 h, concentration afforded the crude amino lactam as its trifluoroacetate

salt. The free amine was obtained by forming a slurry with an excess of solid $NaHCO_3$ in CH_2Cl_2 and allowing to stir for 1 h, at which time the reaction was filtered, the solids were washed with CH_2Cl_2, and the filtrate was concentrated. The resulting residue in CH_2Cl_2 (15 mL) was reacted with the triflate of ethyl *(R)*-2-hydroxy-4-phenylbutyrate (0.0.248 g, 0.73 mmol) and triethylamine (0.1 mL) at room temperature. The reaction was concentrated, partitioned between ethyl acetate and water, and dried over $MgSO_4$. Concentration followed by column chromatography with 1:1 EA/cyclohexane afforded the title compound (0.140 g, 43% overall): $[\alpha]_D = -86.8$ (*c* 0.16, $CHCl_3$); IR (neat) 2920, 2800, 1730, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (m, 1H), 1.27 (t, $J = 6.9$ Hz, 3H), 1.44−1.90 (m, 7H), 2.68 (t, $J = 7.4$ Hz, 2H), 2.82 (m, 1H) 2.99−3.37 (m, 6H), 3.73 (s, 3H), 4.17 (q, $J = 6.9$ Hz, 2H), 5.28 (m, 1H), 7.21−7.31(m, 10H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.5, 27.1, 27.7, 31.6, 31.7, 34.6, 35.1, 46.7, 52.1, 58.7, 59.1, 60.4, 60.6, 125.8, 126.7, 128.3, 128.4, 129.1, 137.2, 147.7, 171.5, 174.5, 175.5; MS (EI) *m/e* 481 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{36}O_5N_2$: C, 69.97; H, 7.55; N, 5.82. Found: C, 69.60; H, 7.68; N, 5.60.

(3*S*,α*R*)-3-[*N*-1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-hexahydro-α-(phenylmethyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (21b). According to the general procedure, lactam **14b** (0.300 g, 0.77 mmol) was converted to the title compound (0.309 g, 84%): $[\alpha]_D = +54.6$ (*c* 0.16, $CHCl_3$); IR (neat) 2920, 2940, 1740, 1730, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, $J = 7.2$ Hz, 3H), 1.24−2.08 (m, 8H), 2.74 (t, $J = 7.3$ Hz, 2H), 2.92−3.42 (m, 6H), 3.73 (s, 3H), 4.20 (m, 2H), 4.80 (dd, $J = 5.2$, 10.5 Hz, 1H), 7.18−7.31 (m, 10H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.3, 27.1, 27.9, 31.6, 31.8, 34.8, 35.1, 48.8, 52.2, 59.1, 59.2, 60.5, 125.8, 126.5, 128.3, 128.4, 128.5, 128.9, 137.6, 141.5, 171.0, 174.6, 175.2; MS (EI) *m/e* 480 (M^+).

(3*S*,α*S*)-3-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-hexahydro-α-(2-methylpropyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (21c). According to the general procedure, lactam **14c** (0.150 g, 0.42 mmol) was converted to **21c** (0.155 g, 83%): IR (neat) ; 2960, 2830, 1730, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, $J = 7.1$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.29 (t, $J = 7.1$Hz, 3 H), 1.62−1.70 (m, 6 H), 1.90−2.10 (m, 6H), 2.74 (m, 2H), 3.20 (m, 1H), 3.32 (t, $J = 8.7$ Hz, 1H), 3.47 (m, 2H), 3.70 (s, 3H), 4.17 (m, 2H), 5.37 (dd, $J = 6.3$, 9.2Hz, 1 H), 7.26 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.3, 21.6, 23.2, 24.9, 26.5, 27.4, 31.7, 32.1, 35.1, 37.6, 43.5, 51.9, 55.1, 59.8, 60.2, 60.6, 125.8, 128.3, 128.4, 141.4, 172.4, 174.5, 175.3; MS (EI) *m/e* 446 (M^+), 447 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{38}O_5N_2$: C, 67.23; H, 8.57; N, 6.27. Found: C, 66.88; H, 8.90; N, 5.98.

(3*S*,α*R*)-3-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-hexahydro-α-(2-methylpropyl)-2-oxo-1*H*-azepine-1-acetic Acid Methyl Ester (21d). According to the general procedure, lactam **14d** (0.100 g, 0.28 mmol) afforded the title compound (0.059 g, 47%): $[\alpha]_D = +13.2$ (*c* 1.00, $CHCl_3$); IR (neat) 2900, 2940, 2830, 1730, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.3$, 3H), 1.41 (m, 1H), 1.52−2.01 (m, 11H), 2.74 (m, 2H), 3.30 (m, 4H), 3.68 (s, 3H), 4.15 (m, 2H), 5.29 (dd, $J = 4.5$, 10.2 Hz, 1H), 7.26 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.7, 22.2, 23.5, 25.4, 27.7, 28.3, 32.4, 33.0, 35.4, 38.6, 45.8, 52.4, 56.8, 60.4, 60.9, 61.0, 126.2, 128.7, 128.8, 141.9, 172.7, 174.9; MS (EI) 446 (M^+) 447 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{38}O_5N_2$: C, 67.23; H, 8.57; N, 6.27. Found: C, 66.73; H, 8.74, N, 6.18.

General Procedure for Saponification to the Diacid. 1-[1(*S*)-(Phenylmethyl)carboxymethyl]-3(*S*)-[[1(*S*)-carboxy-3-phenylpropyl]amino]-perhydroazepin-2-one (22a). Compound **21a** (0.080 g, 0.16 mmol) was dissolved in MeOH (2 mL) and THF (10 mL). NaOH (1 N) (10 mL) was added and the reaction stirred for 48 h at room temperature. The reaction was adjusted to pH 3 using 1 N HCl. Extraction with chloroform, concentration, and recrystallization with *n*-hexane afforded **22a** (0.039 g, 57%): mp 127 °C; IR (KBr) 3400, 3000, 2900, 2820, 1720, 1730, 1650 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.95 (m, 1H), 1.16 (m, 1H), 1.37−1.94 (m, 4H), 1.87 (m, 3H), 2.53 (m, 1H), 2.67 (m, 1H), 3.04−3.38 (m, 6H), 5.00 (m, 1H), 7.14−7.30 (m, 10H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 25.1, 25.9, 26.2, 28.5, 31.1, 31.6, 34.1, 46.7, 58.5, 61.4, 67.0, 126.0, 126.4, 128.2, 128.3, 128.4, 129.1, 137.8, 141.0, 171.6 (signal-to-noise ratio not high enough to observe the two unaccounted carbonyl peaks); MS (EI) *m/e* 439 ($M^+ + 1$); HRMS calcd for ($M^+ + 1$) $C_{25}H_{31}N_2O_5$: 439.2233; found: 439.2241.

1-[1(*S*)-(Phenylmethyl)carboxymethyl]-3(*S*)-[[1(*R*)-carboxy-3-phenylpropyl]amino]-perhydroazepin-2-one (22b). According to the general procedure, compound **21b** (0.100 g, 0.21 mmol) was converted to the title compound as a white solid (0.035 g, 38%): mp 127 °C; IR (KBr) 3800, 3200, 2900, 2820, 1740, 1730, 1650 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.17−2.30 (m, 8H), 2.51 (br s, 1H), 2.61−2.75 (m, 2H), 2.91−3.28 (m, 4H), 3.48 (br s, 1H), 3.78 (d, $J = 5.1$ Hz, 1H) 4.80 (m, 1H), 7.19−7.31 (m, 10H), 10.2 (center of very br s, 2H); ^{13}C NMR (124.8 MHz, DMSO-d_6) δ 26.2, 26.4, 28.9, 31.3, 32.7, 34.2, 48.4, 58.8, 58.9, 62.3, 126.0, 126.3, 128.3 (2), 128.4, 128.9, 138.1, 141.2, 171.5, 171.9, 172.5; MS (EI) *m/e* 439 ($M^+ + 1$); HRMS calcd for ($M^+ + 1$) $C_{25}H_{31}N_2O_5$: 439.2233; found: 439.2247.

1-[1(*S*)-(Phenylmethyl)carboxymethyl]-3(*S*)-[[1(*S*)-carboxy-2-methylpropyl]amino]-perhydroazepin-2-one (22c). According to the general procedure, compound **21c** (0.85 g, 0.19 mmol) was converted to **22c** (0.30 g, 39%): mp 105 °C dec; IR (KBr) 3400, 3100, 2900, 2830, 1740, 1735, 1650 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, $J = 6.2$ Hz, 3H), 0.85 (d, $J = 6.3$ Hz, 3H), 1.26 (m, 4H), 1.64 (m, 5H), 1.90 (m, 2H), 2.33 (m, 2H), 3.18−3.50 (m, 3H), 3.42 (m, 1H), 3.94 (m, 1H), 5.05 (dd, $J = 4.90$, 15.2 Hz, 1H), 7.21 (m, 5H); ^{13}C NMR (124 MHz, DMSO-d_6) δ 21.2, 22.3, 24.3, 26.7, 29.3, 30.8, 33.4, 35.8, 43.2, 59.3, 60.0, 68.9, 125.8, 128.2, 128.3, 141.5, 172.2, 172.7, 173.5; MS (EI) *m/e* 405 ($M^+ + 1$); HRMS calcd for ($M^+ + 1$) $C_{22}H_{33}N_2O_5$: 405.2389; found: 405.2414.

1-[1(*S*)-(Phenylmethyl)carboxymethyl]-3(*S*)-[[1(*R*)-carboxy-2-methylpropyl]amino]-perhydroazepin-2-one (22d). According to the general procedure, compound **21d** (0.059 g, 0.13 mmol) afforded **22d** as a white solid (0.032 g, 61%): mp 110 °C; IR (KBr): 3400, 2940, 2820, 1740, 1730, 1650 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (d, $J = 6.1$ Hz, 3H), 0.90 (d, $J = 10.7$ Hz, 3H), 1.22−2.15 (m, 11H), 2.63 (m, 1H), 2.79 (m, 1H), 3.30 (m, 1H), 3.57(m, 2H), 4.24 (d, $J = 10.6$ Hz, 1H), 4.86 (br t, $J = 5.2$ Hz, 1H), 7.17−7.31 (m, 5H); ^{13}C NMR (124.8 MHz, DMSO-d_6) δ 21.7, 23.0, 24.5, 26.3, 26.7, 28.0, 30.7, 32.0, 37.5, 57.2, 59.0, 59.1, 126.0, 128.2, 128.3, 140.8, 170.6, 172.1; MS (CI) *m/e* 405 ($M^+ + 1$); HRMS calcd for ($M^+ + 1$) $C_{22}H_{33}N_2O_5$: 405.2389; found: 405.2401.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **4e** or **5e** (isomers 1 and 2), **8**, **10f** + **12f**, **11f** or **13f**, and **22a**−**d** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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