Peptidomimetic Synthesis: A Novel, Highly Stereoselective Route to Substituted Freidinger Lactams

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Abstract: New methodology for the synthesis of substituted seven-membered lactams **3** has been developed. This method allows for the stereoselective introduction of substituents at the C-7 position of the azepinone ring as well as α to the acetic acid side chain. Dehydrative cyclization of dipeptidyl aldehydes **11** affords the corresponding bicyclic fused lactams **12** in good yield and high stereoselectivity. Lewis acid catalyzed reduction of **12** with triethylsilane provides azepinones **16** in homochiral form. Introduction of substituents at the C-7 position was effected by treatment of **12** with various alkyl nucleophiles. The resulting azepinones may be viewed as conformationally restricted dipeptidomimetic surrogates.

Introduction

Incorporation of peptidomimetic surrogates into bioactive molecules has been the focus of intensive research over the last ten years. Replacement of proteinogenic amide bonds with suitable conformationally restricted mimics has the potential to afford information regarding the biologically active conformation of peptides.[1] Such information has been helpful in the elucidation of secondary structural features required for the binding of peptides to their receptors. Enhancement in binding, metabolic stability, and/or bioavailability may also be realized. For example, conformationally restrained surrogates have been utilized extensively in the design and synthesis of enzyme inhibitors, often with remarkable success. Restriction of the alanyl-proline dipeptide of enalapril has led to the development of novel and potent ACE inhibitors with increased duration of action and oral bioavailability.[2] Other enzymes in which peptidomimetic replacements have been exploited include renin,[3] neutral endopeptidase,[4] and p21^{ras} farnesyl transferase.[5]

The utilization of γ-, δ-, and ϵ-lactams **2** as conformationally restricted dipeptide surrogates for glycyl dipeptides **1** was pioneered by Freidinger et al.[6] (Figure 1). Consequently, lactams of type **2** are often referred to as "Freidinger lactams." As part of our efforts to develop novel protease inhibitors for the treatment of hypertension and congestive heart failure, our attention has been focused on targets in which the dipeptide portion of an initial lead has been replaced with the constrained peptidomimetic **3**. Critical to our studies was the ability to ascertain the effects of substitution α to the nitrogen on the acetic acid side chain ($R'' \neq H$) in addition to at the C-7 position of the azepinone ring ($R' \neq H$). Alkyl groups at these positions could enhance binding of the molecule through hydrophobic interaction with the enzyme. The presence of these substituents also introduces additional conformational restriction to the molecule, which may lead to increased inhibitory potency as well.

Both stereoselective and stereorandom methods for the generation of γ- and δ-lactam-bridged dipeptides have been described.[7] Unfortunately, current methods for the generation of

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(1) For some recent references, see: (a) Olson, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323-333. (b) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9699-9701. (c) Tourwe, D.; Verschueren, K.; Van Binst, G.; Davis, P.; Porreca, F.; Hruby, V. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1305-1308. (d) Deal, M. J.; Hagan, R. M.; Ireland, S. J.; Jordan, C. C.; McElroy, A. B.; Porter, B.; Ross, B. C.; Stephens-Smith, M.; Ward, P. *J. Med. Chem.* **1992**, *35*, 4195-4204. (e) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672-10674. (f) Callahan, J. F.; Newlander, K. A.; Burgess, J. L.; Eggleston, D. S.; Nichols, A.; Wong, A.; Huffman, W. F. *Tetrahedron* **1993**, *49*, 3479-3488. (g) Genin, M. J.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 860-866. (h) Baldwin, J. E.; Hulme, C.; Edwards, A. J.; Schofield, C. J. *Tetrahedron Lett.* **1993**, *34*, 1665-1668. (i) Ripka, W. C.; DeLucca, G. V.; Bach, A. C., III; Pottorf, R. S.; Blaney, J. M. *Tetrahedron* **1993**, *49*, 3593-3608. (j) Genin, M. J.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 2334-2337. (k) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 256-263. (l) Williams, B. J.; Curtis, N. R.; McKnight, A. T.; Maguire, J. J.; Young, S. C.; Veber, D. F.; Baker, R. *J. Med. Chem.* **1993**, *36*, 2-10.

(2) (a) Parsons, W. H.; Davidson, J. L.; Taub, D.; Aster, S. D.; Thorsett, E. D.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *Biochem. Biophys. Res. Comm.* **1983**, *111*, 166-171. (b) Thorsett, E. D.; Harris, E. E.; Aster, S.; Peterson, E. R.; Taub, D.; Patchett, A. A.; Ulm, E. H.; Lamont, B. I. *Biochem. Biophys. Res. Comm.* **1983**, *117*, 108-113. (c) Attwood, M. R.; Francis, R. J.; Hassall, C. H.; Krohn, A.; Lawton, G.; Natoff, I. L.; Nixon, J. S.; Redshaw, S.; Thomas, W. A. *FEBS Lett.* **1984**, *165*, 201-206. (d) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511-1516. (e) Slade, J.; Stanton, J. L.; Ben-David, D.; Mazzenga, G. C. *J. Med. Chem.* **1985**, *28*, 1517-1521. (f) Reference 8a and b. (g) Attwood, M. R.; Hassall, C. H.; Krohn, A.; Lawton, G.; Redshaw, W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1011-1019. (h) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristram, E. W.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* **1986**, *29*, 251-260. (i) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1987**, *30*, 1984-1991. (j) Bolos, J.; Perez, A.; Gubert, S.; Anglada, L.; Sacristan, A.; Ortiz, J. A. *J. Org. Chem.* **1992**, *57*, 3535-3539. (k) Bolos, J.; Perez-Beroy, A.; Gubert, S.; Anglada, L.; Sacristan, A.; Ortiz, J. A. *Tetrahedron* **1992**, 9567-9576.

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(6) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656-658. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104-109.

(7) (a) Reference 6b. (b) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631-3633. (c) Zydowsky, T. M.; Dellaria, J. F., Jr.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607-5616. (d) Garvey, D. S.; May, P. D.; Nadzan, A. M. *J. Org. Chem.* **1990**, *55*, 936-940. (e) Holladay, M. W.; Nadzan, A. M. *J. Org. Chem.* **1991**, *56*, 3900-3905.

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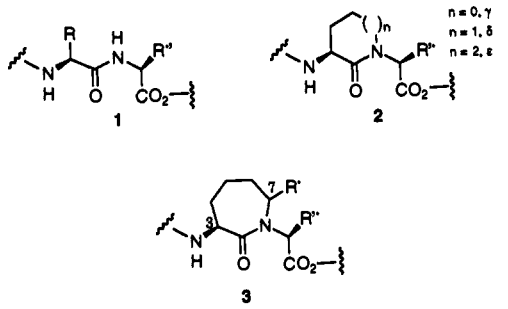
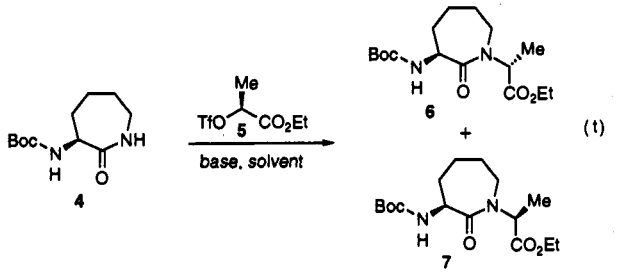


Figure 1. Conformationally restricted dipeptide surrogates.

the corresponding ϵ-lactams do not allow for control of stereochemistry at both the C-3 center[8] and/or the glycyl side chain[9] (where R″ ≠ H). The limitations of the existing methodologies prompted us to develop new routes for the generation of homochiral ϵ-lactams. This methodology permits the synthesis of substituted azepinones in generally good yield with excellent stereocontrol.

Results and Discussion

Initial Alkylation Studies. Early in our studies we sought to utilize *N*-α-Boc-L-α-amino-ϵ-caprolactam[10] (**4**) as the starting material for glycyl-substituted dipeptide surrogate precursors such as **6** or **7** (eq 1). Unfortunately, N-lactam alkylation of **4** with



commercially available ethyl L-2-[(trifluoromethylsulfonyl)oxy]-propionate (**5**) under a variety of conditions invariably produced both **6** *and* **7** as an inseparable mixture of diastereomers. The optimum base for this reaction, lithium hexamethyldisilazide, afforded **6** and **7** in 79% yield but in a 58:42 ratio, respectively. Potassium *tert*-butoxide in THF resulted in an 83:17 mixture of diastereomers, but a lower yield of total product (45%) was realized. The inability of **4** to undergo clean displacement with triflate **5** indicated that other homochiral substrates would likely fail to produce the desired dipeptidyl lactams in a stereospecific manner.

Substituted Azepinones via Bicyclic Lactams. Re-examination of the target molecule **3** led us to consider the readily available amino acid L-(+)-ϵ-hydroxynorleucine[11] as precursor to the ϵ-lactam nucleus (Scheme 1). Substituted glycyl side chains could be incorporated onto this amino acid via standard peptide coupling procedures. We needed only to find conditions effecting cyclization of the resulting dipeptide to the seven-membered lactam ring. Water-soluble carbodiimide coupling of *N*-phthaloyl amino **8** with L- or D-amino esters **9** afforded dipeptides **10** in excellent yields. Attempts to cyclize **10b** or **10c** via Mitsunobu conditions[1g]

Scheme 1

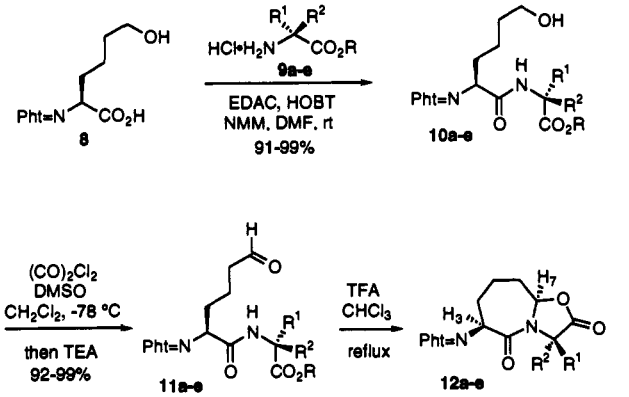


Table 1. Acid-Induced Conversion of Aldehydes **11** to Bicyclic Lactams **12**

	R	R¹	R²	**12** (%)	ratio[a]	time (days)
a	Et	H	H	76	93:7	1.5
b	Et	H	Me	72	93:7	2.5
c	Et	H	CH_2Ph	56	94:6	6
d	Et	CH_2Ph	H	60	96:4	6
e	Me	H	*i*-Pr	68	92:8	19

[a] Diastereomeric ratio at N–C*H*–O bridgehead center as determined by ^1H NMR.

(DIAD, PPh_3), however, failed to give the corresponding lactam. Other attempts based on activation of the hydroxyl group also failed. We consequently decided to convert the alcohol group in **10** to the more "nucleophile accessible" aldehyde. Swern oxidation of **10** gave the corresponding dipeptidyl aldehydes **11** in excellent yields and high diastereomeric purity. It was expected that, under acidic conditions, the desired cyclization would take place by addition of the weakly nucleophilic amide nitrogen to the acid-activated aldehyde functionality. Subsequent dehydration would give the corresponding cyclic enamide **14** (Scheme 2). Unexpectedly, the main product formed from acid-induced cyclization of **11** was bicyclic lactam **12**. The formation of **12** may arise from either trapping of the intermediate *N*-acyliminium species **15** by the carboxy ester followed by loss of the alkyl group (path a) or direct lactonization of the intermediate cyclic hemi-*N*-acylaminal **13** with the proximal alkyl ester (path b). None of these proposed intermediates could be detected in the reaction mixture.

The rate of cyclization was highly dependent upon the steric bulk of the alkyl substituents R¹ and R². Glycyl-derived aldehyde **11a** underwent cyclization in 1.5 days whereas reaction of the bulkier alanyl derivative **11b** took over 2 days to go to completion. For **11e**, the sterically demanding isopropyl substituent severely retarded intramolecular condensation, requiring 19 days for the reaction to go to completion. In this case it was necessary to run the reaction at higher dilution (0.01 M) than normal (0.1–0.05 M) in order to inhibit formation of intermolecular dimerization products.[12] Under these optimized conditions, a 68% yield of

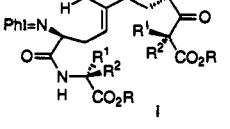
(8) (a) Thorsett, E. D. *Actual. Chim. Ther.* **1986**, *13*, 257–268. (b) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1988**, *31*, 422–428.

(9) Evans, P. A.; Collins, I.; Hamley, P.; Holmes, A. B.; Raithby, P. R.; Russell, K. *Tetrahedron Let.* **1992**, *33*, 6859–6862.

(10) Compound **4** may be prepared by Boc protection of commercially available L-(−)-α-amino-ϵ-caprolactam. Alternately, methylation (Cs_2CO_3, MeI, DMF) of *N*-α-Boc-*N*-ϵ-Cbz-L-lysine followed by hydrogenation (H_2, Pd/C, MeOH) and cyclization (xylenes, reflux, 17 h) gives **4** in 65% overall yield.

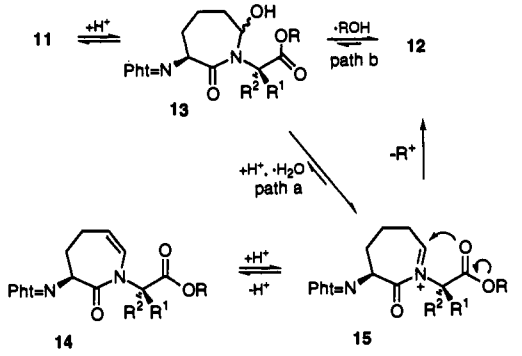
(11) Bodanszky, M.; Martinez, J.; Priestly, G. P.; Gardner, J. D.; Mutt, V. J. *J. Med. Chem.* **1978**, *21*, 1030–1035.

(12) The main side product of the reactions, α,β-unsaturated aldehyde **i**, results from dehydrative aldol condensation of **11** with itself. In the cases



of **11a–d**, formation of this side product was usually <20%. In the case of substrate **11e**, higher dilution conditions were necessary in order to minimize intermolecular condensation of this slow-reacting substrate. The use of a protic acid such as TFA to effect cyclization of **11** to **12** was critical. Treatment of **11b** and **11c** with $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature gave their respective dimers **i** as the exclusive product.

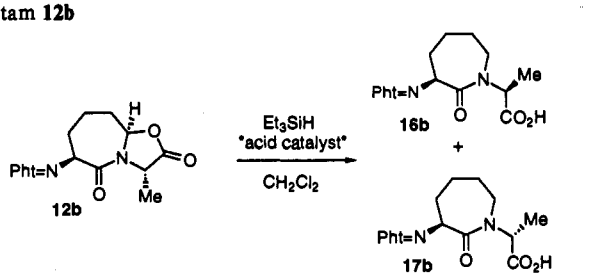
Scheme 2



bicyclic lactam **12e** could be realized. Lactams **12a–e** were formed in high diastereoselectivity, regardless of the nature or stereochemistry of the alkyl substituents, implying that the stereochemistry at the bridgehead center is directed by the orientation of the phthalimido group. Diastereomeric mixtures (at the bridgehead carbon) of **12b** were found to re-equilibrate under the reaction conditions, indicating that diastereomeric composition of the products was subject to thermodynamic rather than kinetic control. The stereochemistries of the major isomers of **12** were assigned on the basis of the presence of a strong NOE between the bridgehead (H_7) and the methine (H_3) hydrogens, clearly indicating a *cis* relationship between these two protons. The internuclear distance between H_3 and H_7 in energy-minimized structures, as determined by Macromodel MM2 calculations,[13] was approximately 2.5 Å. Single-crystal X-ray analysis allowed the unambiguous stereochemical assignment of **12e**.[14] The observed interatomic distance between H_3 and H_7 in **12e** was found to be 2.1 Å.

Reduction of Bicyclic Lactams. With an expedient synthesis of the bicyclic lactams in hand, we next devoted our attention to optimizing the subsequent reduction step necessary for the conversion of **12** to the desired substituted monocyclic lactams. Initial studies were performed on compound **12b** (Table 2). Utilization of basic hydride reducing agents ($LiAlH_4$, DIBAL-H, AlH_3, etc.) would have been incompatible with the phthalimido protecting group. We therefore employed triethylsilane under acidic conditions in hopes of reducing the *N*-acyliminium intermediate of **12b** *in situ*. Treatment of **12b** either with excess triethylsilane in neat refluxing TFA or with $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature slowly but cleanly effected reduction of the C–O lactone bond. Unfortunately substantial epimerization was observed, affording inseparable mixtures of **16b** and **17b**. Starting material was recovered unchanged, indicating that either the reactive *N*-acyliminium species or the product itself was prone to epimerization under these conditions.

Table 2. Effect of Lewis Acid on Et_3SiH Reduction of Bicyclic Lactam **12b**

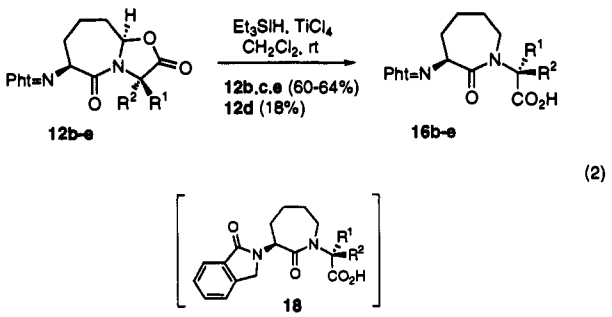


acid	temp (°C)	time (h)	% yield[a] **16b** + **17b**	ratio **16b**/**17b**
TFA (neat)	70	20	66 (100)	50:50
$BF_3{\cdot}OEt_2$	25	64	48 (100)	67:33
$TiCl_4$	25	18	64 (79)	>98:2

[a] Yields in parentheses are based on recovered, unchanged **12b**.

In contrast, $TiCl_4$-catalyzed reduction[15] of **12b** gave exclusively **16b** in an isolated 64% yield. Both $SnCl_4$ and $SnBr_4$ were found to be much less effective. The difference in the stereochemical outcome of the $TiCl_4$ reaction may indicate that reduction of **12b** occurs by direct hydride displacement of the activated lactone C–O bond rather than by reduction of an intermediate, epimerization-prone, *N*-acyliminium species. Alternately, the titanium carboxylate, generated upon reduction of the lactone moiety, may be protected from racemization relative to a free carboxylic acid.

Following this optimized procedure, bicyclic lactams **12b**, **12c**, and **12e** were converted to their corresponding monocyclic azepinones in good yields (eq 2). Lactam **12d** was sluggish to



(2)

reduce under these conditions, affording **16d** in only 18% yield after 65 h. Alternate methods for the reduction of **12d** are being explored. Reduction of **12a** was not studied, since the corresponding azepinone may be readily generated by alkylation of amino caprolactams related to **4**.[16]

The only major side products formed in the $Et_3SiH/TiCl_4$ reductions were the readily separable lactams **18**, arising from reduction of the phthalimido protecting group. Interestingly, the formation of **18** was not observed in the presence of the other acid catalysts studied (TFA, CF_3SO_3H, $BF_3{\cdot}OEt_2$, $SnCl_4$, $SnBr_4$).

Generation of C-7 Substituted Azepinones. The reactivity of the C–O lactone bond in **12** under Lewis acid catalysis provided an avenue for introduction of substituents at the C-7 position of the lactam ring (Scheme 3). Thus treatment of **12a** with allyltrimethylsilane[17] in the presence of $SnBr_4$ afforded in high yield lactam **19** as a single diastereomer. Single-crystal X-ray analysis[14] of its methyl ester **20** confirmed that introduction of the allyl group had taken place with inversion.[18] Under similar conditions, 3-(trimethylsilyl)cyclohexene reacted with **12a** to afford **21** as a 5:1 mixture of diastereomers. Catalytic hydrogenation of the mixture provided the corresponding C-7 cyclohexyl substituted azeopinone **22** as a single diastereomer in 63% overall yield, confirming the stereochemical homogeneity of the lactam ring at the C-7 center.

In contrast to allylsilanes, trimethylaluminum transferred a methyl group with only modest selectivity to **12a** in the presence of $SnCl_4$, affording a 1.8:1 mixture of diastereomers **23**. The minor isomer possessed the *R* configuration at the C-7 position of the lactam ring as determined by the presence of a strong NOE

(13) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. MacroModel—An Integrated Software System for Modeling Organic and Bioorganic Molecules Using Molecular Mechanics. *J. Comput. Chem.* **1990**, *11*, 440. MM2 MacroModel V3.5.

(14) The authors have deposited atomic coordinates for compounds **12e**, **20**, and **26** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, CB2 1EZ U.K.

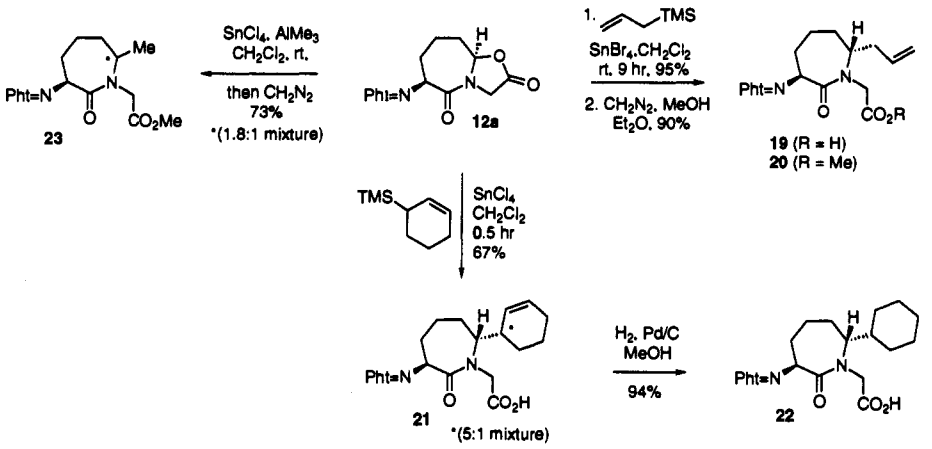
(15) Meyers, A. I.; Synder, L. *J. Org. Chem.* **1993**, *58*, 36–42.

(16) Lactam **4** cleanly undergoes alkylation with ethyl bromoacetate in THF using $LiN(TMS)_2$ as base.

(17) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295–1298.

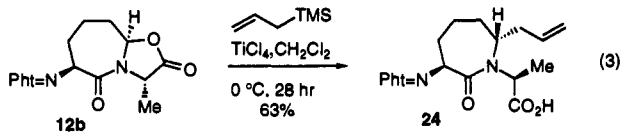
(18) This result parallels work done by Meyers et al. in which reaction of allyltrimethylsilane with a 5,5-fused bicyclic lactam in the presence of $TiCl_4$ gave the corresponding allylated δ-lactam with inversion of stereochemistry; see: (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859.

Scheme 3



between the C-3 and C-7 methine protons. In the major isomer, the formal inversion product of **12a**, a strong NOE was observed between the C-3 methine and the C-7 methyl group. Replacement of $SnCl_4$ with $TiCl_4$ resulted in decomposition of the starting material with no formation of the corresponding methyl adducts.

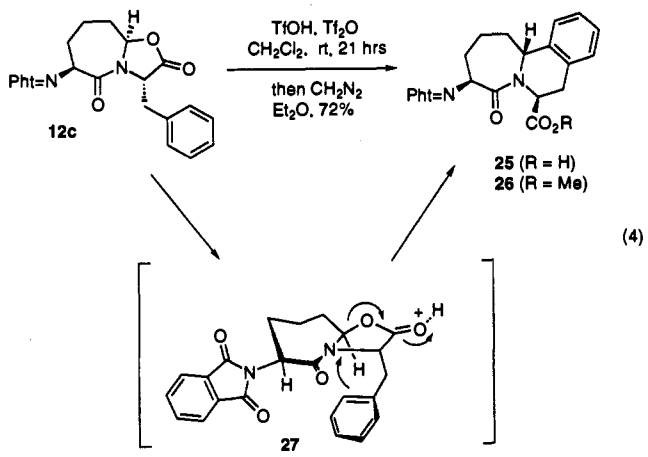
Highly substituted lactam **24** was prepared in good yield by treatment of allyltrimethylsilane with **12b** in the presence of $TiCl_4$ (eq 3). In this case, the use of SnX_4 (X = Cl, Br) resulted in



(3)

slower reaction times and slightly lower yields. The presence of the additional methyl group in **12b**, versus **12a**, is likely responsible for the diminution in reactivity of the substrate due to steric inhibition.

Generation of Benzo-Fused Bicyclic Lactams. Bicyclic lactams of type **12** have proved to be useful intermediates for the generation of substituted monocyclic azepinones. Introduction of substituents has thus far been carried out by the intermolecular addition of groups to the acid-activated lactone portion of the molecule. Inspection of molecular models of **12c** suggests that the appended benzyl functionality was uniquely poised for intramolecular electrophilic addition to the reactive bridgehead carbon (eq 4).



(4)

It had been shown (*vide infra*) that **12c** would not react intramolecularly in the presence of $TiCl_4$ or TFA to give **25**. We were gratified though to discover that treatment of **12c** with the strongly acidic triflic acid afforded, after methylation, benzo-fused bicyclic lactam **26** in good yield. This lactam represents a new conformationally restricted dipeptidomimetic which may be viewed as a mimic of Ala-Phe or Ala-Tic. Unambiguous stereochemical assignment of **26** was obtained by single-crystal X-ray analysis.[14] The high stereoselectivity of the reaction may be rationalized by clean inversion of the N,O-acetal center via attack of the proximal aromatic ring, as depicted in **27**. Speckamp et al.[19] was able to effect a similar intramolecular electrophilic addition of an aromatic group to a reactive *N*-acyliminium ion, also in high diastereoselectivity.

Conclusion

Peptidomimetic research and the utilization of conformationally restricted peptides in the generation of bioactive molecules is currently an active field of study. Unfortunately many of the methods available to generate dipeptide mimetics are nonstereoselective or fail to afford the desired compounds in enantiomerically pure form. The method described herein makes possible the synthesis of substituted 3-aminoazepinones of type **3** in homochiral form. Bicyclic lactams **12**, generated in four steps from L-ε-hydroxynorleucine and commercially available amino esters, are ideal precursors for a variety of substituted monocyclic lactams. Reduction of **12** affords azepinones **16** as single enantiomers in high diastereomeric purity. Introduction of alkyl groups at the C-7 position of the azepinone ring via electrophilic alkylation gives densely substituted compounds such as **24**. In addition, triflic acid induced cyclization of bicyclic lactam **12c** effects the generation of tricycle **26**, a new class of conformationally restricted dipeptide mimetic.

The lactams obtained from these reactions are differentially protected at both the amine and carboxylic acid functionalities, allowing flexibility for elaboration at either the N or C terminus. Conversion of the N-phthalimido protected amino esters to their corresponding amines is readily effected by treatment with hydrazine in methanol. Utilization of these amines for the synthesis of protease inhibitors will be the subject of a future disclosure. Extension of this methodology toward the stereoselective synthesis of δ- and γ-lactams of type **2** (where $n = 0$ and 1), utilizing aspartic and glutamic acid as starting materials, is also planned. In addition, studies involving the use of bicyclic lactams **12** for the synthesis of azepinones substituted at both the C-6 and C-7 positions are in progress and will be reported in due course.

Experimental Section

All reactions were carried out under a static atmosphere of argon and stirred magnetically unless otherwise noted. All reagents used were of commercial quality and were obtained from Aldrich Chemical Co. or

(19) Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969–7972.

Sigma Chemical Co. DMF was obtained from American Burdick and Jackson and used without purification. Dry CH_2Cl_2 was obtained by distillation from CaH_2 under nitrogen. Triflate **5** was purchased from the Aldrich Chemical Company. Melting points were obtained on a Hoover Uni-melt melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Sirius 100-FTIR spectrophotometer. ^1H (400 Mz) and ^{13}C (100 Mz) NMR spectra were recorded on a JEOL GSX400 spectrometer using Me_4Si as an internal standard. 500-MHz ^1H NMR spectra were recorded on a JEOL GSX500 spectrometer. All proton spectral data reported were recorded at 400 MHz unless otherwise stated. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer 241 polarimeter, and c is expressed in g/100 mL. Analytical HPLC was run on a Shimadzu LC-6A series HPLC system using high-pressure mixing. Unless otherwise noted, analyses were run at a flow rate of 1.5 mL/min on a 6.0 × 150 mm² YMC S3 ODS column, using linear binary gradient elution from 50% to 90% aqueous methanol containing 0.2% phosphoric acid over 20 min. Detection was by ultraviolet absorbance at 220 nm unless noted. All flash chromatographic separations were performed using E. Merck silica gel (60, particle size 0.040–0.063 mm). Reactions were monitored by TLC using 0.25-mm E. Merck silica gel plates (60 F_{254}) visualized with UV light or 5% phosphomolybdic acid in 95% EtOH.

(*S*)-6-Hydroxy-2-phthalimidohexanoic Acid (8). A solution of L-ε-hydroxynorleucine (20.00 g, 136 mmol) and Na_2CO_3 (14.43 g, 136 mmol) in H_2O (220 mL) was treated with solid *N*-carbethoxyphthalimide (29.81 g, 136 mmol). After being stirred at room temperature for 2 h, the solution was filtered, cooled in an ice bath, and acidified with 6 N HCl. The resulting precipitate was collected by filtration, washed with H_2O, and subsequently dried overnight *in vacuo* (P = 0.5 mm Hg) at 75 °C to give **8** (29.54 g, 78%) as a white solid: $[\alpha]_D$ −35.7° (*c* 1.3, MeOH); mp 162–163 °C; TLC R_f 0.42 (5:95 HOAc/EtOAc); ^1H NMR (CD_3OD) δ 1.35 (m, 2H), 1.57 (m, 2H), 2.24 (m, 2H), 3.51 (t, J = 6.4 Hz, 2H), 4.84 (dd, J = 4.9 and 10.8 Hz, 1H), 7.80–7.95 (m, 4H); ^{13}C NMR (CD_3OD) δ 172.66, 169.25, 135.65, 133.02, 124.34, 62.54, 53.28, 32.87, 29.49, 23.91; IR (KBr) 3445, 1713, 1393, 716 cm⁻¹. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.84; H, 5.43; N, 5.01.

General Procedure for the Synthesis of Dipeptides 10. A. (*S*)-*N*-(6-Hydroxy-1-oxo-2-phthalimidohexyl)-L-alanine Ethyl Ester (10b, R = Et, R^1 = H, R^2 = Me). A solution of L-alanine ethyl ester hydrochloride (**9b**, R = Et, 1.865 g, 12.1 mmol) and 4-methylmorpholine (NMM, 1.70 mL, 1.56 g, 15.5 mmol) in DMF (27 mL) was treated with acid **8** (2.512 g, 9.06 mmol) and 1-hydroxybenzotriazole hydrate (HOBT·xH_2O, 1.258 g, 9.3 mmol). The mixture was cooled in an ice bath and subsequently treated with 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDAC, 2.091 g, 10.9 mmol). After 1 h at 0 °C and 1.5 h at room temperature, the mixture was partitioned between H_2O and EtOAc. The EtOAc extract was washed successively with H_2O, 0.5 N HCl, H_2O, 50% saturated aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4), filtered, and concentrated to give pure **10b** (3.11 g, 91%) as a white oily foam: TLC R_f 0.23 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.40 (d, J = 7.3 Hz, 3H), 1.41 (m, 2H), 1.61 (m, 2H), 2.21 (m, 1H), 2.34 (m, 1H), 3.61 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.56 (m, 1H), 4.85 (dd, J = 5.5 and 10.7 Hz, 1H), 6.85 (d, J = 6.4 Hz, 1H), 7.72 (m, 2H), 7.87 (m, 2H); ^{13}C NMR δ 172.74, 168.40, 168.03, 134.23, 131.57, 123.51, 62.11, 61.44, 54.39, 48.35, 31.64, 28.41, 22.63, 18.12, 13.93; IR ($CHCl_3$ film) 1717, 1670, 1535, 1385 cm⁻¹; HRMS (FAB) calcd for $C_{19}H_{25}N_2O_6$ (M + H)⁺ 377.1712, found 377.1705.

B. (*S*)-*N*-(6-Hydroxy-1-oxo-2-phthalimidohexyl)glycine ethyl ester (10a, R = Et, R^1 = R^2 = H): oily foam obtained in 98% yield from **8** and glycine ethyl ester hydrochloride (**9a**, R = Et); TLC R_f 0.34 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.39 (m, 2H), 1.59 (m, 2H), 2.14 (s, 1H), 2.23 (m, 1H), 2.34 (m, 1H), 3.60 (t, J = 6.2 Hz, 2H), 4.02 (d, J = 5.1 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.88 (dd, J = 5.5 and 10.7 Hz, 1H), 6.98 (brs, 1H), 7.75 (m, 2H), 7.85 (m, 2H); ^{13}C NMR δ 169.61, 169.18, 168.09, 134.29, 131.51, 123.56, 62.10, 61.49, 54.39, 41.50, 31.59, 28.40, 22.60, 13.98; IR (neat) 1715, 1674, 1539, 1385, 1204 cm⁻¹; HRMS (FAB) calcd for $C_{18}H_{23}N_2O_6$ (M + H)⁺ 363.1557, found 364.1544.

C. (*S*)-*N*-(6-Hydroxy-1-oxo-2-phthalimidohexyl)-L-phenylalanine ethyl ester (10c, R = Et, R^1 = H, R^2 = CH_2Ph): oily foam obtained in 97% yield from **8** and L-phenylalanine ethyl ester hydrochloride (**9c**, R = Et); TLC R_f 0.30 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 1.32 (m, 2H), 1.57 (m, 2H), 2.11 (m, 1H), 2.28 (m, 1H), 3.10 (m, 2H), 3.57 (brs, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.73–4.90 (m, 2H), 6.58 (d, J = 7.7 Hz, 1H), 7.02–7.23 (m, 5H), 7.76 (m, 2H), 7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.19, 168.37, 167.94, 135.69, 134.28, 131.57, 129.24, 128.37, 126.93, 123.59, 62.23, 61.54, 54.42, 53.30, 37.69, 31.70, 28.19, 22.60, 13.99; IR ($CHCl_3$ film) 1717, 1680, 1385 cm⁻¹; HRMS (FAB) calcd for $C_{25}H_{29}N_2O_6$ (M + H)⁺ 453.2026, found 453.2021.

D. (*S*)-*N*-(6-Hydroxy-1-oxo-2-phthalimidohexyl)-D-phenylalanine ethyl ester (10d, R = Et, R^1 = CH_2Ph, R^2 = H): oily foam obtained in 99% yield from **8** and D-phenylalanine ethyl ester hydrochloride (**9d**, R = Et); TLC R_f 0.10 (4:6 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.3 Hz, 3H), 1.32–1.42 (m, 3H), 1.57 (m, 2H), 2.11 (m, 1H), 2.31 (m, 1H), 3.08 (dd, J = 5.8 and 13.9 Hz, 1H), 3.17 (dd, J = 5.8 and 13.9 Hz, 1H), 3.59 (pseudo q, J = 6.0 Hz, 2H), 4.17 (q, J = 7.3 Hz, 2H), 4.77–4.87 (m, 2H), 6.73 (d, J = 7.7 Hz, 1H), 7.03–7.16 (m, 5H), 7.75 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.17, 168.48, 168.04, 135.67, 134.26, 131.56, 129.29, 128.29, 126.90, 123.56, 62.19, 61.57, 54.73, 53.33, 37.51, 31.62, 28.37, 22.63, 14.02; IR ($CHCl_3$ film) 1715, 1680, 1385, 1213 cm⁻¹; HRMS (FAB) calcd for $C_{25}H_{29}N_2O_6$ (M + H)⁺ 453.2026, found 453.2015.

E. (*S*)-*N*-(6-Hydroxy-1-oxo-2-phthalimidohexyl)-L-valine Methyl ester (10e, R = Me, R^1 = H, R^2 = isopropyl): oil obtained in 99% yield from **8** and L-valine methyl ester hydrochloride (**9e**, R = Me); TLC R_f 0.53 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.38 (m, 2H), 1.58 (m, 2H), 2.10–2.41 (m, 4H), 3.59 (m, 2H), 3.66 (s, 3H), 4.56 (dd, J = 4.7 and 8.6 Hz, 1H), 4.90 (dd, J = 5.6 and 10.3 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.75 (m, 2H), 7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.21, 168.98, 168.10, 134.30, 131.51, 123.56, 62.11, 57.24, 54.68, 52.06, 31.62, 31.19, 28.57, 22.65, 18.82, 17.61; IR (CH_2Cl_2 film) 1717, 1676, 1534, 1385, 721 cm⁻¹; HRMS (FAB) calcd for $C_{20}H_{27}N_2O_6$ (M + H)⁺ 391.1869, found 391.1883.

General Procedure for the Synthesis of Dipeptides 11. A. (*S*)-*N*-(1,6-Dioxo-2-phthalimidohexyl)-L-alanine Ethyl Ester (11b, R = Et, R^1 = H, R^2 = Me). A −78 °C solution of oxalyl chloride (930 μL, 1.35 g, 10.7 mmol) in CH_2Cl_2 (30 mL) was treated dropwise with a solution of dry DMSO (1.50 mL, 1.65 g, 21.1 mmol) in CH_2Cl_2 (1.5 mL). After 10 min, a solution of compound **10b** (3.088 g, 8.2 mmol) in CH_2Cl_2 (15 mL) was added dropwise to the above mixture. Fifteen minutes after the addition, TEA (6.8 mL) was added and the mixture was stirred at −78 °C for 10 min and then warmed to 0 °C. The mixture was partitioned between EtOAc/Et_2O and H_2O. The organic layer was washed successively with 1 N HCl and brine and then dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (1:1 acetone/hexanes as eluant) afforded aldehyde **11b** (2.86 g, 93%) as an oil: TLC R_f 0.32 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.41 (d, J = 7.3 Hz, 3H), 1.65 (m, 2H), 2.21 (m, 1H), 2.32 (m, 1H), 2.51 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.56 (m, 1H), 4.84 (dd, J = 5.6 and 10.8 Hz, 1H), 6.77 (d, J = 6.8 Hz, 1H), 7.75 (m, 2H), 7.87 (m, 2H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 201.28, 172.64, 167.94, 134.37, 131.53, 123.66, 61.51, 54.07, 48.45, 42.89, 28.14, 18.77, 18.18, 13.99; IR ($CHCl_3$ film) 1717, 1682, 1383 cm⁻¹; HRMS (FAB) calcd for $C_{19}H_{23}N_2O_6$ (M + H)⁺ 375.1556, found 375.1570.

B. (*S*)-*N*-(1,6-Dioxo-2-phthalimidohexyl)glycine ethyl ester (11a, R = Et, R^1 = R^2 = H): oil obtained in 99% yield from **10a**; TLC R_f 0.50 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.3 Hz, 3H), 1.64 (m, 2H), 2.22 (m, 1H), 2.32 (m, 1H), 2.51 (m, 2H), 4.02 (d, J = 5.1 Hz, 2H), 4.18 (q, J = 7.3 Hz, 2H), 4.87 (dd, J = 5.6 and 10.2 Hz, 1H), 6.89 (brs, 1H), 7.76 (m, 2H), 7.86 (m, 2H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 210.47, 169.46, 168.72, 167.94, 134.37, 131.47, 123.62, 61.47, 53.98, 42.85, 41.50, 28.03, 18.71, 13.98; IR (CH_2Cl_2 film) 1715, 1684, 1535, 1385, 1202 cm⁻¹; HRMS (FAB) calcd for $C_{18}H_{21}N_2O_6$ (M + H)⁺ 361.1400, found 361.1395.

C. (*S*)-*N*-(1,6-Dioxo-2-phthalimidohexyl)-L-phenylalanine ethyl ester (11c, R = Et, R^1 = H, R^2 = CH_2Ph): oily foam obtained in 92% yield from **10c**; TLC R_f 0.45 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.3 Hz, 3H), 1.55 (m, 2H), 2.22 (m, 1H), 2.34 (m, 1H), 2.45 (m, 2H), 3.10 (m, 2H), 4.14 (q, J = 7.3 Hz, 2H), 4.76 (dd, J = 5.8 and 10.0 Hz, 1H), 4.83 (m, 1H), 6.53 (d, J = 7.7 Hz, 1H), 7.01–7.18 (m, 5H), 7.77 (m, 2H), 7.88 (m, 2H), 9.71 (t, J = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 201.29, 171.04, 167.93, 167.74, 135.60, 134.30, 131.43, 129.11, 128.27, 126.86, 123.56, 61.44, 53.97, 53.22, 42.83, 37.58, 27.78, 18.66, 13.92; IR ($CHCl_3$ film) 1717, 1684, 1385, 1200, 721 cm⁻¹; HRMS (FAB) calcd for $C_{25}H_{27}N_2O_6$ (M + H)⁺ 451.1869, found 451.1872.

D. (*S*)-*N*-(1,6-Dioxo-2-phthalimidohexyl)-D-phenylalanine ethyl ester (11d, R = Et, R^1 = CH_2Ph, R^2 = H): oil obtained in 96% yield from **10d**; TLC R_f 0.45 (1:1 acetone/hexane); ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H), 1.60 (m, 2H), 2.12 (m, 1H), 2.30 (m, 1H), 2.46 (m, 2H), 3.08 (dd, J = 5.8 and 13.9 Hz, 1H), 3.17 (dd, J = 5.8 and 13.9 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 4.76–4.86 (m, 2H), 6.73 (d, J = 7.7 Hz, 1H),

7.02–7.17 (m, 5H), 7.75 (m, 2H), 7.85 (m, 2H), 9.70 (t, J = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 201.24, 171.01, 168.05, 167.89, 135.61, 134.32, 131.46, 129.21, 128.27, 126.87, 123.59, 61.51, 54.36, 53.31, 42.79, 37.48, 27.96, 18.74, 13.98; IR (CH_2Cl_2 film) 1777, 1717, 1684, 1528, 1385, 712 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{27}N_2O_6$ (M + H)$^+$ 451.1869, found 451.1886.

E. (*S*)-*N*-(1,6-Dioxo-2-phthalimidohexyl)-L-valine methyl ester (11e, R = Me, R^1 = H, R^2 = isopropyl): oil obtained in 95% yield from **10e**; TLC R_f 0.63 (1:1 acetone/hexane); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.63 (m, 2H), 2.19–2.40 (m, 2H), 2.52 (m, 2H), 3.67 (s, 3H), 4.58 (dd, J = 5.1 and 8.6 Hz, 1H), 4.89 (dd, J = 5.6 and 10.3 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 7.77 (m, 2H), 7.88 (m, 2H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 201.70, 172.41, 168.82, 168.31, 134.74, 131.79, 123.98, 57.60, 54.65, 52.41, 43.20, 31.52, 28.59, 19.07, 17.95; IR (CH_2Cl_2 film) 2965, 1770, 1717, 1684, 1530, 1385, 721 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{25}N_2O_6$ (M + H)$^+$ 389.1713, found 389.1726.

TFA-Induced Cyclization of Aldehydes 11. A. (6*S*)-*trans*-Tetrahydro-2,5-dioxo-6-phthalimidooxazolo[3,2-*a*]azepine-2,5(3*H*,6*H*)-dione (12a, R^1 = R^2 = H). A solution of aldehyde **11a** (5.16 g, 14.3 mmol) and trifluoroacetic acid (TFA, 40 mL) in $CHCl_3$ (160 mL) was refluxed for 40 h under argon. The cooled solution was neutralized with saturated aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The pooled organic layers were washed with brine, dried (Na_2SO_4), filtered, and stripped. The residue was filtered through a short plug of silica gel, eluting with 1:1 EtOAc/CH_2Cl_2. Concentration of the solvent followed by trituration of the residue with Et_2O afforded bicyclic lactam **12a** (3.44 g, 76%) as a white solid in 97% diastereomeric purity: $[\alpha]_D$ +43.0° (c 1.3, $CHCl_3$); mp 239–240 °C; TLC R_f 0.51 (1:1 acetone/hexane); ^{1}H NMR ($CDCl_3$) δ 1.72–1.95 (m, 2H), 2.10 (m, 1H), 2.25 (m, 1H), 2.41 (m, 1H), 2.78 (m, 1H), 4.28 (m, 2H), 4.77 (dd, J = 1.7 and 12.0 Hz, 1H), 5.84 (d, J = 10.2 Hz, 1H), 7.74 (m, 2 H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.61, 166.79, 166.35, 134.21, 131.70, 123.56, 90.72, 54.66, 45.04, 34.73, 29.08, 24.78; IR (KBr) 1804, 1713, 1670, 1391, 1362 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.79; H, 4.42; N, 8.69.

B. [3*S*-(3α,6β,9aα)]-Tetrahydro-3-methyl-2,5-dioxo-6-phthalimidooxazolo[3,2-*a*]azepine-2,5(3*H*,6*H*)-dione (12b, R^1 = H, R^2 = Me). A solution of aldehyde **11b** (4.12 g, 11.0 mmol) and TFA (32 mL) in $CHCl_3$ (220 mL) was refluxed under argon for 2.5 days. The solvent was removed by rotary evaporation, and the residue was azeotroped twice with CH_2Cl_2. Flash chromatography (15:85 acetone/CH_2Cl_2 as eluant) afforded bicyclic lactam **12b** (2.59 g, 72%) as a white solid in 93% diastereomeric purity. Analytically and diastereomerically pure material was obtained by recrystallization from EtOAc/CH_2Cl_2: $[\alpha]_D$ +103.1° (c 0.36, $CHCl_3$); mp 250–251 °C; TLC R_f 0.33 (1:1 acetone/hexane); ^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 6.8 Hz, 3H), 1.73 (m, 1H), 1.85 (m, 1H), 1.99 (m, 1H), 2.21 (m, 1H), 2.43 (m, 1H), 2.78 (m, 1H), 4.52 (q, J = 6.8 Hz, 1H), 4.74 (dd, J = 1.9 and 12.2 Hz, 1H), 5.84 (d, J = 10.2 Hz, 1H), 7.72 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.27, 167.85, 166.29, 134.18, 131.75, 123.54, 89.73, 55.17, 52.61, 35.46, 28.75, 24.41, 16.12; IR (KBr) 1798, 1715, 1678, 1397, 1354 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 61.19; H, 4.91; N, 8.53. Found: C, 61.95; H, 4.74; N, 8.36.

C. [3*S*-(3α,6β,9aα)]-Tetrahydro-2,5-dioxo-3-(phenylmethyl)-6-phthalimidooxazolo[3,2*a*]azepine-2,5(3*H*,6*H*)-dione (12c, R^1 = H, R^1 = CH_2Ph). A solution of aldehyde **11c** (6.11 g, 13.5 mmol) and TFA (34 mL) in $CHCl_3$ (205 mL) was refluxed under argon for 6 days. Workup as in **12a** followed by flash chromatography of the residue (40–60% EtOAc in hexane as eluant) afforded bicyclic lactam **12c** (3.075 g, 56%) as a white foam in 94% diastereomeric purity. An additional 0.74 g of recovered unreacted **11c** was also isolated: TLC R_f 0.37 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 2.01–2.27 (m, 3H), 2.76 (m, 1H), 3.06 (d, J = 13.7 Hz, 1H), 3.67 (dd, J = 5.5 and 13.7 Hz, 1H), 4.51–4.61 (m, 2H), 4.81 (d, J = 5.1 Hz, 1H), 7.05–7.48 (m, 5H), 7.80 (m, 2H), 7.94 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.45, 166.70, 134.39, 134.28, 130.02, 129.73, 129.09, 127.74, 123.65, 90.48, 59.15, 55.63, 35.28, 33.61, 28.68, 24.25; IR ($CHCl_3$ film) 1802, 1717, 1667, 1389, 1350 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{21}N_2O_5$ (M + H)$^+$ 405.1450, found 405.1434. Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.25; H, 5.34; N, 6.47.

D. [3*R*-(3α,6α,9aβ)]-Tetrahydro-2,5-dioxo-3-(phenylmethyl)-6-phthalimidooxazolo[3,2-*a*]azepine-2,5(3*H*,6*H*)-dione (12d, R^1 = CH_2Ph, R^2 = H). A solution of aldehyde **11d** (4.57 g, 10.1 mmol) and TFA (30 mL) in $CHCl_3$ (160 mL) was refluxed under argon for 6 days. Workup as in the case of **12a** followed by flash chromatography of the residue (1:1 EtOAc/hexane as eluant) afforded bicyclic lactam **12d** (2.47 g, 60%) as a white foam in 96% diastereomeric purity. An additional 1.01 g of recovered unreacted **11d** was also isolated: TLC R_f 0.39 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ –0.15 (m, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 1.84 (m, 2H), 2.57 (m, 1H), 3.24 (dd, J = 1.7 and 13.7 Hz, 1H), 3.58 (dd, J = 6.4 and 13.7 Hz, 1H), 4.66 (dd, J = 1.5 and 11.7 Hz, 1H), 4.71 (dd, J = 1.7 and 6.4 Hz, 1H), 5.57 (d, J = 10.7 Hz, 1H), 7.20–7.48 (m, 5H), 7.73–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.47, 166.33, 135.17, 134.13, 130.41, 128.79, 128.67, 127.56, 123.46, 90.07, 58.07, 54.67, 34.27, 32.62, 28.37, 24.72; IR ($CHCl_3$ film) 1802, 1713, 1672, 1391, 1356 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{21}N_2O_5$ (M + H)$^+$ 405.1450, found 405.1445.

E. [3*S*-(3α,6β,9aα)]-Tetrahydro-3-(1-methylethyl)-2,5-dioxo-6-phthalimidooxazolo[3,2-*a*]azepine-2,5(3*H*,6*H*)-dione (12e, R^1 = H, R^2 = isopropyl). A solution of aldehyde **11e** (9.50 g, 23.8 mmol) and TFA (70 mL), in $CHCl_3$ (2.4 L) was refluxed under argon for 19 days. Workup as in the case of **12b** followed by flash chromatography of the residue (15:85 acetone/hexane as eluant) afforded bicyclic lactam **12e** (5.74 g, 68%) as a white solid in 92% diastereomeric purity. Recrystallization from CH_2Cl_2/Et_2O afforded fine needles of diastereomerically pure **12e** which were suitable for X-ray crystallographic analysis: $[\alpha]_D$ +93.5° (c 0.88, $CHCl_3$); mp 204–206 °C; TLC R_f 0.73 (1:1 acetone/hexane); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.72 (m, 1H), 1.85 (m, 1H), 2.09–2.28 (m, 2H), 2.44 (m, 1H), 2.63–2.85 (m, 2H), 4.46 (d, J = 3.4 Hz, 1H), 4.77 (dd, J = 1.7 and 12.4 Hz, 1H), 5.81 (d, J = 9.8 Hz, 1H), 7.72 (m, 2H), 7.86 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 168.86, 167.93, 166.26, 134.15, 131.80, 123.50, 90.21, 61.70, 55.38, 35.93, 28.49, 28.06, 24.30, 17.71, 16.14; IR (KBr), 1802, 1719, 1663, 1391, 1364, 1213, 719 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.98; H, 5.61; N, 7.76.

Et_3SiH Reduction of Bicyclic Lactams 12. A. [*S*-(*R,*R**)]-Hexahydro-α-methyl-2-oxo-3-phthalimido-1*H*-azepine-1-acetic Acid (16b, R^1 = H, R^2 = Me)**. A solution of **12b** (1.013 g, 3.08 mmol) and Et_3SiH (4.0 mL, 2.91 mmol, 25.0 mmol) in dry CH_2Cl_2 (36 mL) at room temperature was treated with $TiCl_4$ (1.0 M in CH_2Cl_2, 6.1 mL, 6.1 mmol). After 18 h, H_2O was added to the yellow, turbid mixture to quench the reaction, and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give an oil. The residue was flash chromatographed (EtOAc followed by 2:98 HOAc/EtOAc as eluant) to give acid **16b** (646 mg, 64% (79% based on 202 mg of recovered starting material)) as a white foam. Crystallization from EtOAc/hexane afforded analytically pure material: $[\alpha]_D$ = +6.2° (c 0.24, $CHCl_3$); mp 161–163 °C; TLC R_f 0.51 (5:95 HOAc/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 7.2 Hz, 3H), 1.70 (m, 1H), 1.88 (m, 1H), 2.03–2.19 (m, 2H), 2.71 (m, 1H), 3.37–3.58 (m, 2H), 5.02 (dd, J = 1.5 and 11.4 Hz, 1H), 5.15 (q, J = 7.2 Hz, 1H), 7.69 (m, 2H), 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.35, 170.95, 168.21, 133.98, 132.07, 123.43, 54.65, 46.14, 29.28, 28.65, 27.60, 14.81; IR ($CHCl_3$ film) 1713, 1655, 1389, 719 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.64; H, 5.41; N, 8.47.

B. [*S*-(*R,*R**)]-Hexahydro-2-oxo-α-(phenylmethyl)-3-phthalimido-1*H*-azepine-1-acetic Acid (16c, R^1 = H, R^2 = CH_2Ph)**. A solution of **12b** (1.400 g, 3.46 mmol), Et_3SiH (4.4 mL, 3.20 g, 27.5 mmol), and 1.0 M $TiCl_4$ (7.0 mL, 7.0 mmol) in CH_2Cl_2 (42 mL) was stirred at room temperature for 66 h. Workup and purification as in the case of **16b** afforded acid **16c** (870 mg, 62%) as a white foam. HPLC analysis showed **16c** to be 99.2% diastereomerically pure (**16c**/**16d** = 124:1): $[\alpha]_D$ –52.4° (c 2.1, $CHCl_3$); TLC R_f 0.57 (HOAc/EtOAc); HPLC t_R = 14.43 min; ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 1H), 1.46–1.60 (m, 2H), 1.80–1.95 (m, 2H), 2.57 (m, 1H), 3.16 (dd, J = 5.1 and 15.4 Hz, 1H), 3.28 (m, 2H), 3.52 (dd, J = 11.5 and 15.4 Hz, 1H), 4.64 (m, 1H), 4.87 (d, J = 11.5 Hz, 1H), 7.00–7.42 (m, 5H), 7.70 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.68, 171.38, 167.93, 137.22, 133.93, 132.04, 129.47, 128.70, 126.94, 123.40, 65.45, 54.43, 50.82, 34.56, 29.15, 28.55, 26.43; IR (KBr) 1715, 1661, 1391, 719 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{23}N_2O_5$ (M + H)$^+$ 407.1607, found 407.1599.

C. [*R*-(*R,*S**)]-Hexahydro-2-oxo-α-(phenylmethyl)-3-phthalimido-1*H*-azepine-1-acetic Acid (16d, *R*^{1} = CH_2Ph, R^2 = H)**. A solution of **12d** (700 mg, 1.73 mmol), Et_3SiH (2.20 mL, 1.60 g, 13.8 mmol), and 1.0 M $TiCl_4$ (3.45 mL, 3.45 mmol) in CH_2Cl_2 (18 mL) was stirred at room temperature for 64 h. Workup and purification as in the case of **16b** afforded acid **16d** (128 mg, 18%) as a white foam. HPLC analysis showed **16d** to be 98.2% diastereomerically pure (**16d**/**16c** = 55:1): TLC R_f 0.38 (2:98 HOAc/EtOAc); HPLC t_R = 14.92 min; ^{1}H NMR ($CDCl_3$) δ 1.30–1.72 (m, 3H), 1.98 (m, 2H), 2.49 (m, 1H), 2.96 (m, 1H), 3.13–3.45 (m, 3H), 4.72 (m, 1H), 4.98 (d, J = 11.1 Hz, 1H), 7.13–7.50 (m, 5H), 7.71 (m, 2H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.86, 172.22, 169.28,

138.38, 134.99, 133.15, 130.06, 129.80, 127.84, 124.50, 64.38, 55.62, 50.72, 35.57, 29.80, 29.53, 29.11; IR (KBr) 1715, 1661, 1391, 721 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{23}N_2O_5$ (M + H)$^+$ 407.1607, found 407.1622.

D. [S-(R*,R*)]-Hexahydro-α-(1-methylethyl)-2-oxo-3-phthalimido-1H-azepine-1-acetic Acid (16e, R¹ = H, R² = isopropyl). A solution of **12e** (500 mg, 1.4 mmol), Et_3SiH (1.84 mL, 1.34 g, 11.5 mmol), and 1.0 M $TiCl_4$ (2.75 mL, 2.75 mmol) in CH_2Cl_2 (17 mL) was stirred at room temperature for 40 h. Workup and purification as in the case of **16b** afforded acid **16e** (300 mg, 60%) as a white foam: $[\alpha]_D$ −30.0° (*c* 0.5, $CHCl_3$); TLC R_f 0.72 (5:95 HOAc/EtOAc); ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 1.66 (m, 2H), 1.92 (m, 1H), 2.12 (d, *J* = 11.5 Hz, 2H), 2.27 (m, 1H), 2.70 (m, 1H), 3.45–3.69 (m, 2H), 4.73 (d, *J* = 10.3 Hz, 1H), 5.06 (d, *J* = 10.7 Hz, 1H), 7.71 (m, 2H), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.37, 171.85, 168.21, 133.98, 131.99, 123.41, 64.52, 54.57, 45.99, 29.02, 28.57, 27.57, 27.36, 19.67, 19.03; IR (KBr) 3434, 2965, 1715, 1661, 1391, 719 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{23}N_2O_5$ (M + H)$^+$ 359.1607, found 359.1590.

Generation of C-7 Substituted Lactams. A. (3S)-trans-Hexahydro-2-oxo-3-phthalimido-7-(2-propenyl)-1H-azepine-1-acetic Acid (19). A solution of **12a** (2.600 g, 8.27 mmol) and allyltrimethylsilane (10.0 mL, 7.2, g, 62.9 mmol) in CH_2Cl_2 (75 mL) was treated at room temperature with $SnBr_4$ (1.0 M in CH_2Cl_2, 16.5 mL, 16.5 mmol). After 9 h, the clear, colorless solution was quenched with H_2O and extracted with EtOAc/Et_2O. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (2:98 HOAc/EtOAc as eluant) provided **19** (2.810 g, 95%) as a white foam: TLC R_f 0.55 (5:95 HOAc/EtOAc); ^1H NMR ($CDCl_3$) δ 1.85–2.21 (m, 5H), 2.57 (m, 1H), 2.69–2.88 (m, 2H), 3.54 (brs, 1H), 3.73 (d, *J* = 18.0 Hz, 1H), 4.63 (d, *J* = 18.0 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 5.26 (d, *J* = 17.0 Hz, 1H), 5.76 (m, 1H), 7.70 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.60, 170.87, 168.52, 134.19, 133.82, 132.26, 123.62, 119.16, 61.49, 55.21, 53.19, 36.44, 30.87, 28.88, 22.58; IR (KBr) 1715, 1647, 1391, 719 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{21}N_2O_5$ (M + H)$^+$ 357.1450, found 357.1448.

Treatment of **19** in CH_2Cl_2/Et_2O with dicyclohexylamine resulted in the formation of the corresponding DCHA salt of **19**: $[\alpha]_D$ = −7.2° (*c* 1.0, $CHCl_3$); mp 192–194 °C. Anal. Calcd for $C_{31}H_{43}N_3O_5 \cdot 0.3H_2O$: C, 68.56; H, 8.09; N, 7.74. Found: C, 68.27; H, 8.02; N, 7.49.

B. (3S)-trans-Hexahydro-2-oxo-3-phthalimido-7-(2-propenyl)-1H-azepine-1-acetic Acid Methyl Ester (20). A solution of **19** (2.500 g, 7.0 mmol) in MeOH (20 mL) and Et_2O (30 mL) was treated with excess ethereal diazomethane in Et_2O for 10 min at 0 °C. The excess diazomethane was destroyed by the addition of HOAc, and the solvent was removed by rotary evaporation. Flash chromatography (1:1 EtOAc/hexane as eluant) provided methyl ester **20** as a solid. Recrystallization from CH_2Cl_2/Et_2O provided 2.334 g (90%) of analytically pure compound **20**: $[\alpha]_D$ = −12.4° (*c* 2.0, $CHCl_3$); mp 107–109 °C; TLC R_f 0.29 (1:1 EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.86–2.20 (m, 5H), 2.57 (m, 1H), 2.70–2.85 (m, 2H), 3.51 (m, 1H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.71 (s, 3H), 4.66 (d, *J* = 17.5 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.26 (d, *J* = 15.4 Hz, 1H), 5.73 (m, 1H), 7.70 (m, 2H), 7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.34, 169.90, 168.29, 133.90, 133.73, 132.09, 123.36, 118.82, 61.02, 55.06, 52.73, 52.12, 36.26, 30.67, 28.71, 22.40. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.87; H, 6.00; N, 7.52.

C. (3S)-trans-7-(2-Cyclohexen-1-yl)hexahydro-2-oxo-3-phthalimido-1H-azepine-1-acetic Acid (21). A mixture of bicyclic lactam **12a** (332 mg, 1.05 mmol) and 3-(trimethylsilyl)cyclohexene[20] (1.08 g, 7.0 mmol) in CH_2Cl_2 (14 mL) was cooled in an ice bath and then treated dropwise with $SnCl_4$ (1.0 M in CH_2Cl_2, 2.11 mL, 2.11 mmol). The cooling bath was removed, and the resulting slurry was stirred at room temperature for 35 min. The mixture was quenched by the addition of H_2O and extracted with EtOAc. The organic extract was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (EtOAc followed by 2% HOAc in ETOAc) afforded **21** (279 mg, 67%) as a 5:1 mixture of diastereomers (as determined by HPLC): TLC R_f 0.44 (5:95 HOAc/EtOAc); HPLC t_R = 16.68 min (15.5%) and 9.22 min (82.7%); ^1H NMR for major isomer (270 MHz, $CDCl_3$) δ 1.37 (m, 1H), 1.56–2.32 (m, 10H), 2.79 (m, 1H), 2.98 (m, 1H), 3.23 (m, 1H), 3.61 (d, *J* = 17.0 Hz, 1H), 4.81 (dd, *J* = 17.0 Hz, 1H), 5.10 (dd, *J* = 12.0 and 2.4 Hz, 1H), 5.60 (m, 1H), 5.88 (m, 1H), 7.70 (m, 2H), 7.84 (m, 2H); ^{13}C NMR for major isomer (67.7 MHz, $CDCl_3$) δ 174.26, 170.92, 168.35, 133.91, 131.98, 130.33, 126.41, 123.35, 65.46, 54.76, 53.84, 36.16, 28.37, 28.20, 25.72, 25.25, 22.31, 20.73; IR ($CHCl_3$ film) 1773, 1715, 1651, 1387, 719 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{25}N_2O_5$ (M + H)$^+$ 397.1763, found 397.1758.

D. (3S)-trans-7-Cyclohexylhexahydro-2-oxo-3-phthalimido-1H-azepine-1-acetic Acid (22). A mixture of compound **21** (5:1 mixture, 254 mg, 0.64 mmol) and Pd on carbon (10%, 85 mg) in MeOH (15 mL) was hydrogenated (balloon) at room temperature for 6 h. HPLC shows essentially one peak at 18.31 min (96.7%). The reaction was filtered through Celite, concentrated, and then flash chromatographed (2:98 HOAc/EtOAc) to give diastereomerically pure **22** (240 mg, 94%) as a white foam: TLC R_f 0.47 (3:97 HOAc/EtOAc); ^1H NMR ($CDCl_3$) δ 0.93 (m, 2H), 1.18 (m, 1H), 1.39 (m, 2H), 1.60–2.22 (m, 11H), 2.74 (m, 1H), 3.08 (m, 1H), 3.53 (d, *J* = 17.5 Hz, 1H), 4.81 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 7.71 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.31, 171.16, 168.50, 134.04, 132.15, 123.46, 67.23, 54.81, 54.19, 38.85, 30.97, 30.19, 28.46, 28.32, 26.19, 25.98, 22.52; IR (CH_2Cl_2 film) 2932, 1773, 1715, 1649, 1387, 719 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_5$ (M + H)$^+$ 399.1920, found 399.1915.

E. (3S)-Hexahydro-7-methyl-2-oxo-3-phthalimido-1H-azepine-1-acetic Acid Methyl Ester (23). A solution of **12a** (315 mg, 1.00 mmol) in dry CH_2Cl_2 (18 mL) was treated first with $SnCl_4$ (1.0 M in CH_2Cl_2, 1.48 mL, 1.48 mmol) followed by $AlMe_3$ (2.0 M in hexane, 1.64 mL, 3.28 mmol). After 2 days at room temperature, the reaction was quenched with H_2O and the homogeneous mixture was diluted with 10% HCl and extracted twice with EtOAc. The EtOAc extract was washed with brine, dried (Na_2SO_4), filtered, and stripped. The residue was dissolved in CH_2Cl_2 (15 mL) and subsequently treated with excess ethereal diazomethane for 5 min. The excess CH_2N_2 was removed by evaporation, and the solvent was concentrated. Flash chromatography of the residue (55:45 EtOAc/hexane as eluant) provided azepinone **23** (253 mg, 73%) as a 1.8:1 mixture of diastereomers (as determined by NMR): TLC R_f 0.24 (1:1 EtOAc/hexane); HPLC t_R = 8.40 min (34.3%) and 9.22 min (63.6%); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, CH_3 (minor)), 1.52 (d, *J* = 6.9 Hz, CH_3 (major)), 1.68–2.13 (m, 5H), 2.62–2.78 (m, 1H), 3.64 (m, N-C*H*-Me (major)), 3.96 (d, *J* = 17.0 Hz, N-CH_2-CO_2Me (major)), 4.02 (m, N-C*H*-Me (minor)), 4.08–4.17 (m, N-CH_2-CO_2Me (minor)), 4.42 (d, *J* = 17.0 Hz, N-CH_2-CO_2Me (major)), 5.05 (d, *J* = 11.9 Hz, Pht=N-C*H*-CO (major)), 5.28 (m, Pht=N-C*H*-CO (minor)), 7.70 (m, 2H), 7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.77, 170.25, 170.07, 169.86, 168.16, 133.82, 132.04, 123.28, 56.49, 54.99, 53.25, 52.95, 52.12, 52.04, 51.91, 43.94, 34.32, 32.91, 29.01, 28.40, 26.30, 22.18, 19.79, 17.26; IR (KBr) 1751, 1715, 1653, 1387, 1209, 721 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{21}N_2O_5$ (M + H)$^+$ 345.1451, found 345.1454.

F. [3S-[1(R*),3α,7β]]-Hexahydro-α-methyl-2-oxo-3-phthalimido-7-(2-propenyl)-1H-azepine-1-acetic Acid (24). Neat $TiCl_4$ (500 μL, 865 mg, 4.56 mmol) was added to a solution of **12b** (93:7 diastereomeric mixture, 500 mg, 1.53 mmol) and allyltrimethylsilane (2.0 mL, 12.2 mmol) in CH_2Cl_2 (22 mL) at 0 °C. After 28 h, the mixture was quenched with H_2O and extracted with EtOAc. The EtOAc extract was washed with brine, dried (Na_2SO_4), filtered, and stripped. Flash chromatography (EtOAc followed by 1:99 HOAc/EtOAc as eluant) of the residue provided acid **24** (357 mg, 63%) as an oil in 93.3% diastereomeric purity (determined by HPLC): TLC R_f 0.65 (2:98 HOAc/EtOAc); HPLC t_R = 12.28 min (6.6%) and 13.28 min (93.3%); ^1H NMR ($CDCl_3$) δ 1.45 (d, *J* = 7.3 Hz, 3H), 1.86–2.09 (m, 4H), 2.54 (m, 1H), 2.68 (m, 1H), 2.83 (m, 1H), 3.48 (m, 1H), 4.96–5.06 (m, 2H), 5.15 (d, *J* = 10.3 Hz, 1H), 5.23 (d, *J* = 16.7 Hz, 1H), 5.76 (m, 1H), 7.68 (m, 2H), 7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.11, 170.98, 168.94, 134.61, 134.57, 132.76, 124.09, 119.04, 58.06, 57.43; 55.80, 37.47, 30.30, 29.56, 23.02, 15.16; IR (KBr) 1775, 1717, 1643, 1391, 721 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{23}N_2O_5$ (M + H)$^+$ 371.1607, found 371.1597.

G. [4S-(4α,7α,12bα)]-1,2,3,4,5,7,8,12b-Octahydro-5-oxo-4-phthalimidoazepino[2,1-a]isoquinoline-7-carboxylic Acid Methyl Ester (26). To a slightly chilled (10 °C) mixture of trifluoromethanesulfonic acid (TfOH, 20 g) and trifluoromethanesulfonic anhydride (Tf_2O, 3.0 mL) was added a solution of **12c** (1.500 g, 3.70 mmol) in CH_2Cl_2 (50 mL). After the pale-yellow homogeneous solution was stirred at room temperature for 21 h, the reaction was poured into ice water and extracted with EtOAc. The organic extract was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in MeOH/CH_2Cl_2 and treated with excess ethereal diazomethane for 15 min. Excess CH_2N_2 was destroyed by the addition of acetic acid. Removal of the solvent followed by recrystallization of the residue from CH_2Cl_2/EtOAc

(20) Prepared from 3-bromocyclohexene according to the method of: Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2055–2061.

afforded **26** (880 mg) as a white solid. An additional 236 mg of pure product was obtained by recrystallization of the mother liquor to give a total of 1.116 g (72%) compound **26**: $[\alpha]_D$ −204.7° (*c* 0.5, $CHCl_3$); mp 254–256 °C; TLC R_f 0.25 (1:1 EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.73 (m, 1H), 1.88 (m, 2H), 2.07 (m, 2H), 2.40 (m, 1H), 3.15–3.27 (m, 2H), 3.41 (s, 3H), 5.08 (m, 2H), 5.95 (dd, J = 4.5 and 11.8 Hz, 1H), 7.10–7.27 (m, 5H), 7.69 (m, 2H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.70, 170.13, 167.39, 137.57, 133.99, 132.11, 131.29, 127.92, 127.47, 127.03, 126.42, 123.43, 55.78, 54.35, 53.74, 51.90, 37.39, 31.04, 26.25, 20.19; IR ($CHCl_3$ film) 1778, 1715, 1640, 1389, 719 cm^{-1}. Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.12; H, 5.05; N, 6.72.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **8**, **10a–e**, **11a–e**, **12a–e**, **16b–e**, **19–24**, and **26**, as well as NOE difference spectra on compounds **12a**, **12b**, **12d**, and **23**, and positional and thermal parameters for the X-ray analyses of compounds **12e**, **20**, and **26** (67 pages).