Conformationally Restricted Peptide Mimetics: The Incorporation of 6,5-Bicyclic Lactam Ring Skeletons into Peptides

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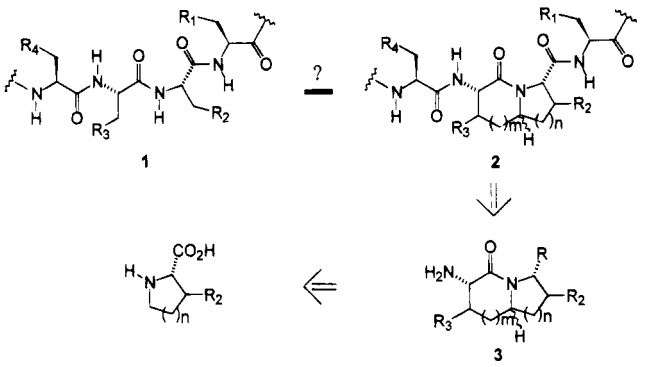
This manuscript describes a convenient procedure for the synthesis of peptide fragments containing 6,5-bicyclic lactam-based conformational constraints. The syntheses capitalize on an electrochemical oxidation to functionalize a substituted proline derivative, an *N*-acyliminium ion-initiated cyclization in order to form a transient seven-membered-ring lactam, and a rearrangement reaction to form the desired six-membered-ring lactam. The bicyclic lactam products were converted into peptide building blocks and the stereochemistry of the building blocks assigned using two-dimensional NMR techniques. Once synthesized, the building blocks were readily incorporated into peptide fragments with the use of standard peptide synthesis techniques. The synthetic route employed was shown to be compatible with both aryl and branched amino acid side chains.

Introduction

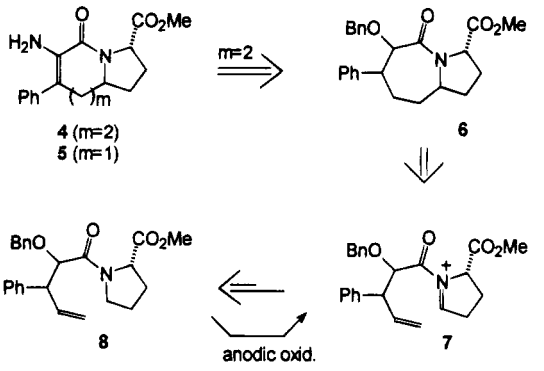
In recent years, a number of groups have been actively pursuing the construction of conformationally restricted peptide mimetics.[1] The goal of this work has been to examine the relationship between the activity predicted for a particular peptide conformation and the actual biological activity observed. In this quest, the use of lactam rings to add rigidity to the peptide backbone has proven quite successful.[2] For our part, we hoped to use peptides, like **2**, containing bicyclic lactam ring skeletons to ask specific questions about the importance of backbone conformation.

In this way, key sections of a peptide backbone could be imbedded into the ring skeleton and the conformation of the backbone controlled by alterations in ring size and bridgehead stereochemistry. However, before such a program could be initiated, a convenient, rapid synthesis of the conformationally restricted peptide analogs was needed. From the start, our approach to this problem was to synthesize building blocks with the general structure of **3** and then to incorporate the building blocks into peptides.[3] We report herein that the discovery of a new rearrangement reaction has led to a general route to 6,5-bicyclic lactam peptide building blocks and their incorporation into peptide fragments.

Scheme 1



Scheme 2



Background

Initially, lactam building blocks **4** and **5** were selected as a targets (Scheme 2). These targets were chosen because of their relationship to a series of lactam-based, computer-designed thyroliberin (TRH) analogs (*vide supra*).[4] The goal of this work was twofold. First, we

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(1) For reviews see: (a) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287. (b) Hölzemann, G. *Kontakte (Darmstadt)* **1991**, *1*, 3. (c) Olson, G. L. et. al. *J. Med. Chem.* **1993**, *36*, 3039. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (e) Wiley, R. A.; Rich, D. H. *Med. Chem. Rev.* **1993**, *13*, 327.

(2) For selected examples of lactam based peptide mimetics: (a) Wolf, J. P.; Rapoport, H. *J. Org. Chem* **1989**, *54*, 3164, as well as references 1–8 therein. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104. (c) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631. (d) Zydowsky, T. M.; Dellaria, J. F., Jr.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607. (e) Kempf, D. J.; Condon, S. L. *J. Org. Chem.* **1990**, *55*, 1390. (f) Kemp, D. S.; McNamara, P. E. *J. Org. Chem.* **1985**, *50*, 5834, and references therein. (g) Nagai, U; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647. (h) Hinds, M. G.; Richards, N. G. J.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1447. (i) Paul, P. K. C.; Burney, P. A.; Campbell, M. M.; Osguthorpe, D. J. *BioMed. Chem. Lett.* **1992**, *2*, 141. (j) Ward, P.; Ewan, G. B.; Jordon, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *33*, 1848. (k) 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. (l) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914. (m) Flynn, G. A.; Burkholder, T. P.; Huber, E. W.; Bey, P. *BioMed. Chem. Lett.* **1991** *1*, 309. (n) Burkholder, T. P.; Huber, E. W.; Flynn, G. A. *BioMed. Chem. Lett.* **1993**, *3*, 231. (o) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 339. (p) Lombart, H. G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (q) Colombo, L.; Giacomo, M. D.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.* **1994**, *35*, 4031.

(3) (a) Moeller, K. D.; Rothfus, S. L.; Wong, P. L. *Tetrahedron* **1991**, *47*, 583. (b) Moeller, D. D.; Rothfus, S. L. *Tetrahedron Lett.* **1992**, *33*, 2913. Moeller, K. D.; Hanau, C. E.; d'Avignon, A. *Tetrahedron Lett.* **1994**, *35*, 825. (c) Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett.* **1994**, *35*, 6989.

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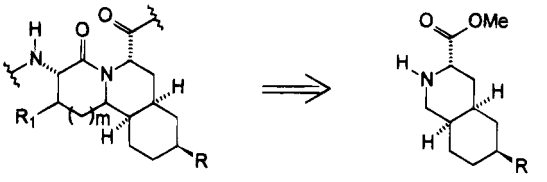
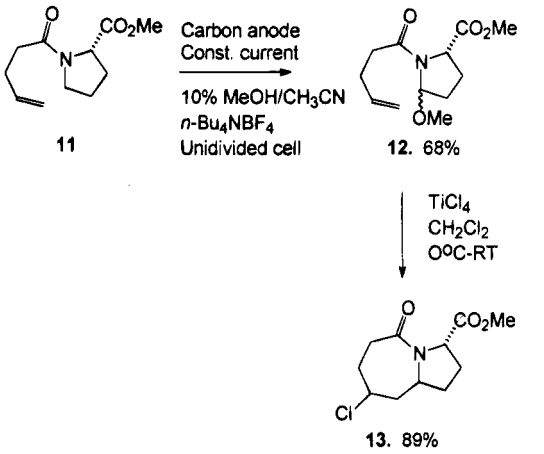
hoped to demonstrate the overall synthetic utility of an electrochemically based method for annulating lactam rings onto simple amino acid derived starting materials,[5,6] and second, we hoped to use the analogs generated in order to test the validity of the active analog approach used to design the analogs.[7]

The main strength of the electrochemical approach chosen centered on the opportunity electrochemistry affords for functionalizing simple amino acid derivatives.[8] As outlined in Scheme 2 for building block **4**, an electrochemical approach would allow for the use of a proline derived amide as the starting material for the synthesis by enabling the *selective* functionalization of the proline ring. The lactam ring would then be constructed by intramolecular trapping of the resulting *N*-acyliminium ion. In this plan, the key chiral center on the five-membered ring of the bicyclic lactam building block would be readily incorporated in the synthesis as part of the starting material. In principle, the extension of such an electrochemical route to more complex peptide systems would simply involve selecting the appropriate amino acid derived starting material. For example, building blocks like **3** (Scheme 1) with R_2 not equal to hydrogen and decahydroisoquinoline derived building blocks like **9** (Scheme 3) could potentially be constructed from existing amino acid derivatives.[9,10]

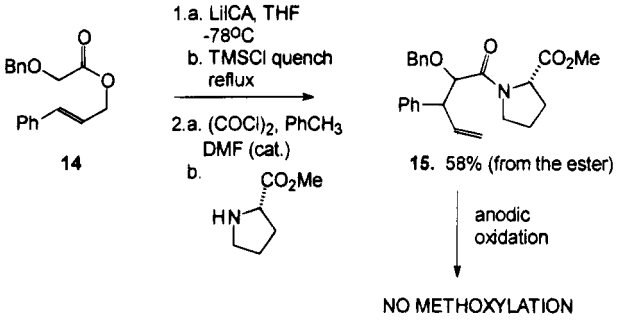
Scheme 3



Scheme 4



Scheme 5



With this in mind, we turned our attention toward constructing building block **4** using an electrochemically based annulation procedure. The seven-membered-ring lactam analog **4** was chosen as our first target because of the relative ease with which the annulation procedure had generated seven-membered-ring lactam-containing ring skeletons in model systems (Scheme 4).[3a] Unfortunately, this chemistry did not work as well in the real system. While the substrate for the electrolysis reaction (**15**) was readily prepared, under no conditions could the amide be oxidized in a satisfactory manner (Scheme 5).[11] In all cases, the starting substrate **15** was recovered in high yield. A series of structure–reactivity studies indicated that the the difficulties associated with the oxidation reaction were a result of both the proline methyl ester *and* the benzyloxy substituent α to the amide carbonyl. Reduction of the methyl ester to a CH_2-OH substituent led to a loss of formaldehyde from the

(4) Font, J. Computer-Assisted Drug Design. Ph.D. Thesis. Washington University, St. Louis, MO, 1986. In addition, recent modeling studies have suggested that both six- and seven-membered-ring lactam analogs about the Phe-Pro amide bond provide suitable overlap with the current model for TRH binding. Previously, only the synthesis of the seven-membered-ring lactam derivatives had been proposed. Unpublished results with Lawrence D. Rutledge.

(5) For pioneering work with anodic amide oxidations see (a) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1964**, *86*, 4139. (b) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Org. Chem.* **1966**, *31*, 128. (c) Ross, S. D.; Finkelstein, M.; Peterson, C. *J. Am. Chem. Soc.* **1966**, *88*, 4657. For reviews see (d) Shono, T. *Tetrahedron* **1984**, *40*, 811. (e) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Syntheses*; Saucy, G., Ed.; Organic Syntheses, Inc., 1984; Vol. 63, p 206 and references therein. (f) Shono, T. In *Topics in Current Chemistry*; Steckhan, E., Ed.; Springer-Verlag: Berlin Heidelberg New York, 1988; Vol. 148, p 131.

(6) For examples of anodic amide oxidation based annulation procedures please see along with reference 3 (a) Ban, Y.; Okita, M.; Wakamatsu, T.; Mori, M. *Heterocycles* **1980**, *14*, 1089. (b) Ban, Y.; Irie, K. *Heterocycles* **1981**, *15*, 201. (c) Ban, Y.; Irie, K. *Heterocycles* **1982**, *18*, 255. (d) Ban, Y.; Okita, M.; Wakamatsu, T. *Heterocycles* **1983**, *20*, 401. (e) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (f) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919. (g) Mori, M.; Kagechika,K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409. (h) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (i) Moeller, K. D.; Tarazi, S.; Marzabadi, M. R. *Tetrahedron Lett.* **1989**, *30*, 1213. (j) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058. (k) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.

(7) For reviews see (a) Marshall, G. R.; Barry, C. D.; Bosshard, H. E.; Dammkoehler, R. A.; Dunn, D. A. In *Computer-Assisted Drug Design*; Olson, E. C.; Christoffersen, R. E., Eds.; American Chemical Society: Washington D. C., 1979; p 205. (b) Marshall, G. R. *Ann. Rev. Pharmacol. Toxicol.* **1987**, *27*, 193. (c) Marshall, G. R.; Motoc, I. In *Molecular Graphics and Drug Design*; Burgen, A. S. V., Roberts, G. C. K., Tute, M. S., Eds.; Elsevier: Amsterdam, 1986; p 115. (d) Marshall, G. R. In *Computer-Aided Molecular Design*; Richards, W. G., Ed., IBC Technical Services: London, 1989; pp 91–104.

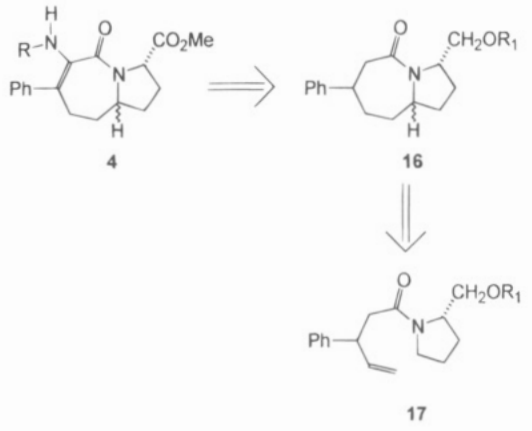
(8) For examples of amide oxidations being used to functionalize peptides see reference 3d as well as (a) Shono, T.; Matsumura, Y.; Inoue, K. *J. Org. Chem.* **1983**, *48*, 1388. (b) Thaning, M.; Wistrand, L.-G. *Helv. Chim. Acta* **1986**, *69*, 1711. (c) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843. (d) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (e) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401. (f) Papadopoulos, A.; Heyer, J.; Ginzel K.-D.; Steckhan, E. *Chem. Ber.* **1989**, *122*, 2159. (g) Ginzel, K.-D.; Brungs, P.; Steckhan, E. *Tetrahedron* **1989**, *45*, 1691. (h) Papadopoulos, A.; Lewall, B.; Steckhan, E.; Ginzel, K.-D.; Knoch, F.; Nieger, M. *Tetrahedron* **1991**, *47*, 563. (i) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1991**, *56*, 2787. (j) Moeller, K. D.; Rutledge, L. D. *J. Org. Chem.* **1992**, *57*, 6360. (k) Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, in press.

(9) For the use of substituted proline derivatives as conformationally restricted amino acid analogs see Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270.

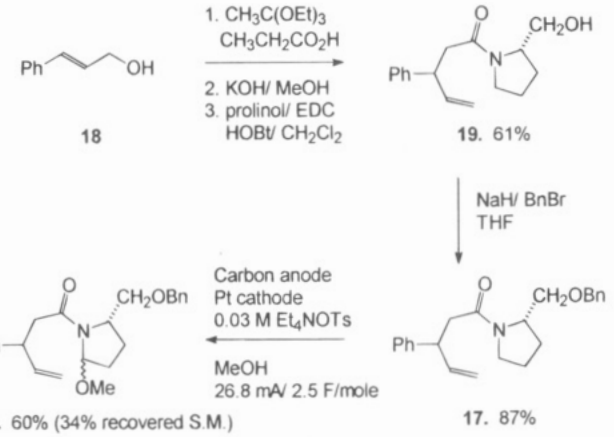
(10) For the use of decahydroisoquinoline derivatives in HIV protease inhibitors see Krohn, A.; Redshaw, S.; Ritchie, J. C.; Graves, B. J.; Hatada, M. H. *J. Med. Chem.* **1991**, *34*, 3340. For the recent syntheses of a series of 6-substituted decahydroisoquinoline-3-carboxylates see Ornstein, P. L.; Augenstein, N. K.; Arnold, M. B. *J. Org. Chem.* **1994**, *59*, 7862.

(11) Unpublished results with Scott L. Rothfus.

Scheme 6



Scheme 7

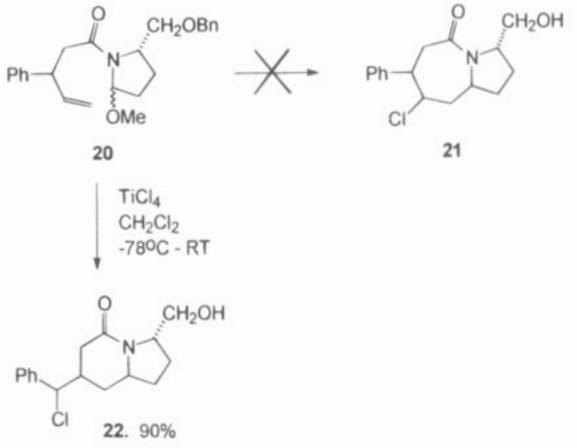


N-acyliminium ion intermediate generated from the electrolysis. Conversion of the methyl ester to a CH_2-OMe substituent did not lead to an increase in the efficiency of the oxidation.[11] Clearly, either the methyl ester or the benzyloxy substituent had to be removed in order to allow for the oxidation and then introduced into the molecule at a later stage. For this reason, the synthesis was redesigned in order to add the functionality α to the amide at a point subsequent to the anodic oxidation reaction (Scheme 6).

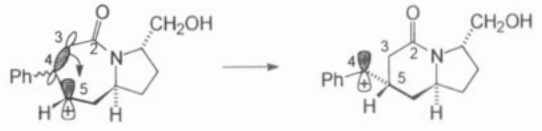
A Surprise Rearrangement and a New Route to Bicyclic Six-Membered-Ring Lactams

The electrolysis substrate **17** needed for the retrosynthesis outlined in Scheme 6 was synthesized from cinnamyl alcohol with the use of an ortho-ester Claisen rearrangement, followed by hydrolysis of the resulting ester, and then coupling of the acid with prolinol (Scheme 7). The substrate synthesis was completed by protection of the prolinol alcohol as the benzyl ether. In the absence of an oxygen substituent on the carbon α to the amide, the electrolysis reaction proceeded without difficulty. In this case, amide **17** was oxidized in an undivided cell equipped with a nitrogen inlet using a carbon rod anode, a platinum wire cathode, a 0.03 M tetraethylammonium tosylate in methanol electrolyte solution, and a constant current of 26.8 mA. After a total of 2.5 F/mol of charge was passed, a 60% isolated yield of the methoxylated product **20** was obtained along with a 34% yield of recovered starting material. An increase in the number of F/mol did not improve the yield of methoxylated product but did reduce the amount of starting material recovered. In these experiments, a product tentatively assigned as a bis-methoxylated material was obtained.

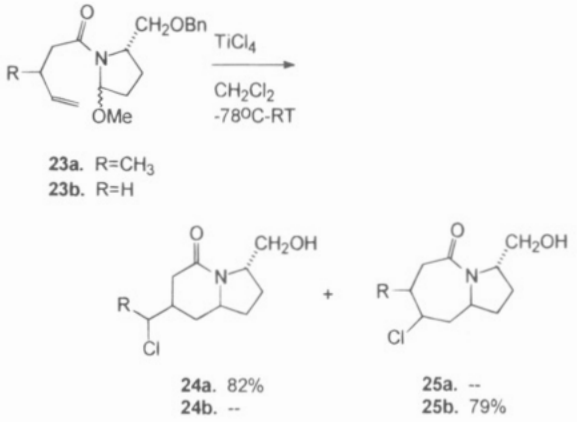
Scheme 8



Scheme 9



Scheme 10

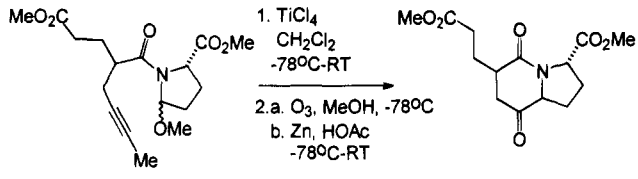


To our surprise, the cyclization reaction did not afford the seven-membered-ring lactam (**21**/ Scheme 8) that we were expecting.[12] Instead the molecule rearranged to form the previously unobserved six-membered-ring lactam products **22** in a 90% isolated yield. A mixture of four diastereomers was obtained. The complete connectivity of all four rearranged products was established with the use of an HMQC-TOCSY experiment.[13] Apparently, the rearranged products formed from initial cyclization to a seven-membered-ring lactam having a secondary carbocation at C_5 (Scheme 9) followed by migration of the C_3-C_4 bond. Trapping of the resulting benzylic carbocation with chloride led to product **22**.

At the time, it was thought that the driving force for the rearrangement reaction was either the relief of seven-membered-ring strain, the generation of a benzylic carbocation, or both. In order to differentiate between these possibilities, substrate **23a** was synthesized and studied (Scheme 10). For details concerning the synthesis of **23a** please see the Experimental Section. In this example, a methyl substituent was placed β to the amide carbonyl in the starting material so that there would be little difference in the stability of the secondary carbocation generated from the initial cyclization and the secondary

(12) For a preliminary account of this work please see reference 3b.
(13) d'Avignon, D. A.; Hanau, C. E.; Fobian, Y. M.; Moeller, K. D. *J. Coord. Chem.* **1994**, *32*, 135.

Scheme 11



26 27. 72%

carbocation generated from the rearrangement reaction. Interestingly, this cyclization also led exclusively to the six-membered-ring lactam product derived from the rearrangement reaction. The identity of the rearranged product was again confirmed with the use of an HMQC-TOCSY experiment. Clearly, the rearrangement reaction was driven by relief of the strain associated with the seven-membered ring. It was not until the starting material without a substituent on the side chain (**23b**) was studied that a seven-membered-ring lactam product could be isolated. Apparently, the rearrangement reaction could not proceed in this case because it would have generated a primary carbocation.

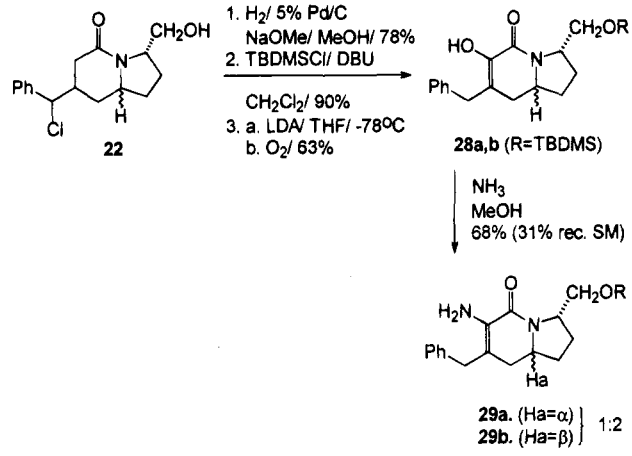
These observations raised two important questions. First, how should the synthesis be altered so that bicyclic peptide mimetics containing seven-membered-ring lactams could be made, and second, could the rearranged product be used to synthesize six-membered-ring lactam peptide building blocks like **5**? With respect to this second question, the rearrangement reaction did suggest an intriguing and potentially powerful route to bicyclic, six-membered-ring lactam ring skeletons that were nicely suited for conversion into peptide mimetics. This was an important observation. One of the reasons the seven-membered-ring lactam had been initially selected for study was that it was expected to be the easier one to make. The seven-membered ring was the case where the double bond could not migrate into conjugation with the carbonyl of the amide. This migration plagued six-membered ring cyclization substrates analogous to **11**.[3a] In addition, the annulation reactions that had led to six-membered-ring lactams utilized disubstituted acetylenes to trap the incipient *N*-acyliminium ions (Scheme 11).[3a,6k] While these reactions proved very useful for making a pair of angiotensin converting enzyme inhibitors, the lactam products formed lacked the substituent β to the amide carbonyl needed for development of building blocks like **5**, and had an extra carbonyl γ to the amide that would need to be removed prior to development of a peptide building block. The rearrangement to form **22** avoided all of these problems.

For this reason, we turned our attention toward determining how the carbon α to the carbonyl in **22** could be functionalized and then converting the resulting product into a building block for incorporation into peptide chains.

Development of a Bicyclic-Lactam-Containing Peptide Fragment

In order to convert the mixture of diastereomeric bicyclic lactams represented by structure **22** into a pair of building blocks that could be utilized for peptide synthesis, the mixture of diastereomers was treated with hydrogen over palladium on carbon in the presence of sodium methoxide in order to cleave the carbon–chlorine bond, the free alcohol protected as a *tert*-butyldimethylsilyl group, and then the carbon α to the amide functionalized by treatment with lithium diisopropylamide followed by quenching with oxygen (Scheme 12). The resulting mixture of ketones **28a** and **28b** was converted into a pair of enamines **29a** and **29b** by treatment with ammonia in methanol. A couple of items with respect to this work deserve further comment. First, we were surprised to find that the functionalization of the carbon α to the amide with LDA and O_2 directly formed the ketone (usually obtained as a mixture of keto- and enol-tautomers) and did not "stop" at the alcohol product. This reaction was specific for six-membered-ring lactams. For other amides, the direct formation of α-keto amide products benefited greatly from the addition of trifluoroacetic anhydride to the reaction mixture before work-up.[14] Second, we were surprised by the stability of the enamine products. The bridgehead isomers **29a** and **29b** (a 1:2 mixture from the cyclization) were both stable on silica gel and could be readily separated by gravity flow chromatography. Isomer **29a** was the less polar of the two compounds.

Scheme 12



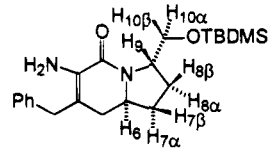
22 28a,b (R=TBDMS)

29a. (Ha=α) 29b. (Ha=β) 1:2

The stereochemistry of **29a** and **29b** was assigned with the use of 2D-NOE experiments. The key features of these assignments are illustrated in Scheme 13. The complete assignment of the proton and carbon of the building blocks was established using an HMQC-TOCSY experiment.[13] Both the assignment of **29a** and the assignment of **29b** hinged on identifying $H_{7\beta}$ and then determining its relationship to H_6. In isomer **29a**, the stereochemistry of $H_{7\beta}$ could be readily assigned because it showed a cross peak across the ring to H_9. Clearly, $H_{7\beta}$ and H_9 were on the same side of the ring. The stereochemistry of H_9 was established in the starting material. The bridgehead proton H_6 showed a cross peak with $H_{7\beta}$ that had a volume integral of 0.26. The magnitude of this interaction was consistent with a trans relationship between vicinal protons and was significantly smaller than the volume integral obtained for the H_6–$H_{7\beta}$ cross peak in isomer **29b** (see below). Unfortunately, it was not possible to establish the relationship between H_6 and $H_{7\alpha}$ for isomer **29a** because the signal for $H_{7\alpha}$ was buried beneath the methylene protons on C_5. The stereochemical assignment of isomer **29b** was made by first establishing the stereochemistry of the H_7 and H_8 methylene protons and then relating these assignments to the bridgehead proton. For **29b**, the cross peak between H_9 and $H_{8\beta}$ had a volume integral of 1.31 whereas the cross peak between H_9 and $H_{8\alpha}$ had a volume integral of 0.25. This pair of cross peaks led to the assignment of a cis relationship between H_9 and $H_{8\beta}$. The

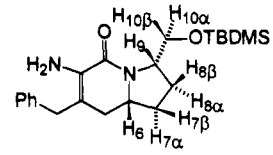
(14) Unpublished results with Yvette M. Fobian.

Scheme 13



29a

Signal One	Signal Two	NOE Crosspeak Volume Integral
H_9	$H_{7\beta}$	0.14
$H_{7\beta}$	H_9	0.30
H_6	$H_{7\beta}$	0.26



29b

Signal One	Signal Two	NOE Crosspeak Volume Integral
H_9	$H_{8\beta}$	1.31
H_9	$H_{8\alpha}$	0.25
$H_{7\alpha}$	H_{10} (one H)	0.51
H_6	$H_{8\beta}$	0.25
H_6	$H_{7\alpha}$	0.27
H_6	$H_{7\beta}$	2.00

stereochemistry of $H_{7\alpha}$ was established with the use of a cross peak between $H_{7\alpha}$ and one of the H_{10} methylene protons. The stereochemistry of the bridgehead proton H_6 was then assigned based on a cross peak between H_6 and $H_{8\beta}$ having a volume integral of 0.25, a cross peak between H_6 and $H_{7\alpha}$ having a volume integral of 0.27, and a cross peak between H_6 and $H_{7\beta}$ having a volume integral of 2.00. The existence of the cross peak to $H_{8\beta}$ and the magnitude of the cross peaks to $H_{7\alpha}$ and $H_{7\beta}$ clearly established H_6 as being on the β-face of the molecule as drawn.

Having established the stereochemistry of isomers **29a** and **29b**, the building blocks were carried on and incorporated into the peptide fragments independently (Scheme 14). For the most part, this work was uneventful and took advantage of standard peptide chemistry. To date, the yields associated with the generation of **31a** have not been optimized. Details of these sequences are given in the Experimental Section.

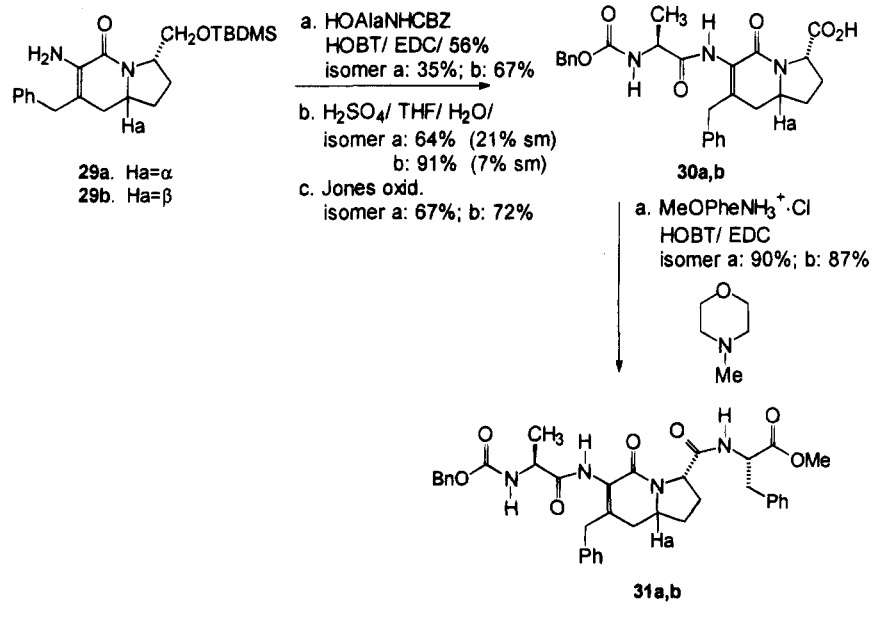
Total Synthesis of a Six-Membered-Ring Lactam-Containing Proline-Leucine Mimetic: Generality of the Approach

One of the questions that arose at this point concerned whether the synthetic route discovered above could be used in a general fashion to make conformationally restricted X-Pro (or X-Y if the proline is substituted) peptide mimetics. In order to address this issue, the synthesis of a six-membered lactam ring based leucine building block was synthesized. The leucine building block was selected as a target in order to determine if the overall strategy was compatible with the incorporation of amino acids with branched side chains.

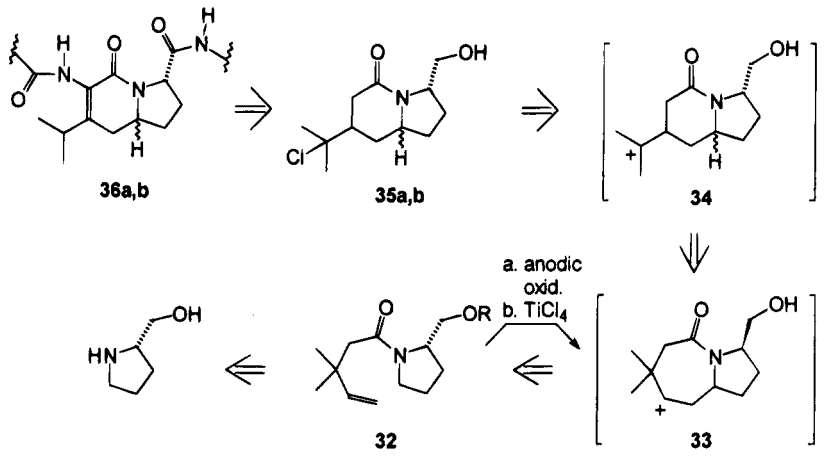
A retrosynthetic analysis for a peptide fragment containing the restricted Leu-Pro unit is illustrated in Scheme 15. As in the earlier synthesis, the key step in this scheme involved functionalization of an amino acid derivative using electrochemistry followed by a titanium tetrachloride initiated cyclization–rearrangement sequence. In this case, the rearrangement was expected to be driven both by the strain associated with the initially formed seven-membered-ring lactam **33** and by the formation of the tertiary carbocation in **34**.

In practice, the synthesis proceeded in a straight forward fashion (Scheme 16). Following preparation of the electrolysis substrate as outlined, anodic oxidation of the amide using a carbon anode, a platinum cathode, a 0.03 M Et_4NOTs in methanol electrolyte solution, an undivided cell, and a constant current of 51.4 mA (2.5 F/mol) led to the formation of a 66% isolated yield of the methoxylated amide along with a 21% yield of the recovered starting material. On the basis of previous experience,[5,6] the reaction was not pushed passed 2.5 F/mol. The titanium tetrachloride-induced cyclization reaction led to the formation of products having a six-membered-ring lactam **35** as anticipated. Following cleavage of the carbon–chloride bond, reprotection of the prolinol-derived alcohol, functionalization of the carbon α to the amide, and conversion to an enamine intermedi-

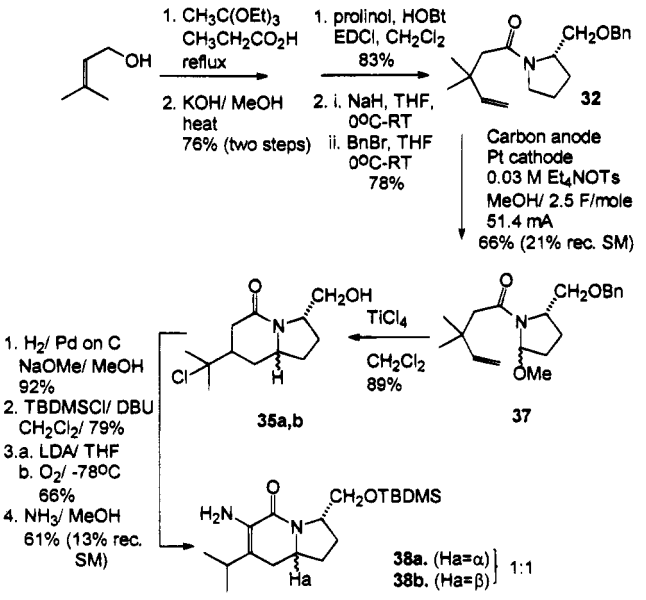
Scheme 14



Scheme 15



Scheme 16

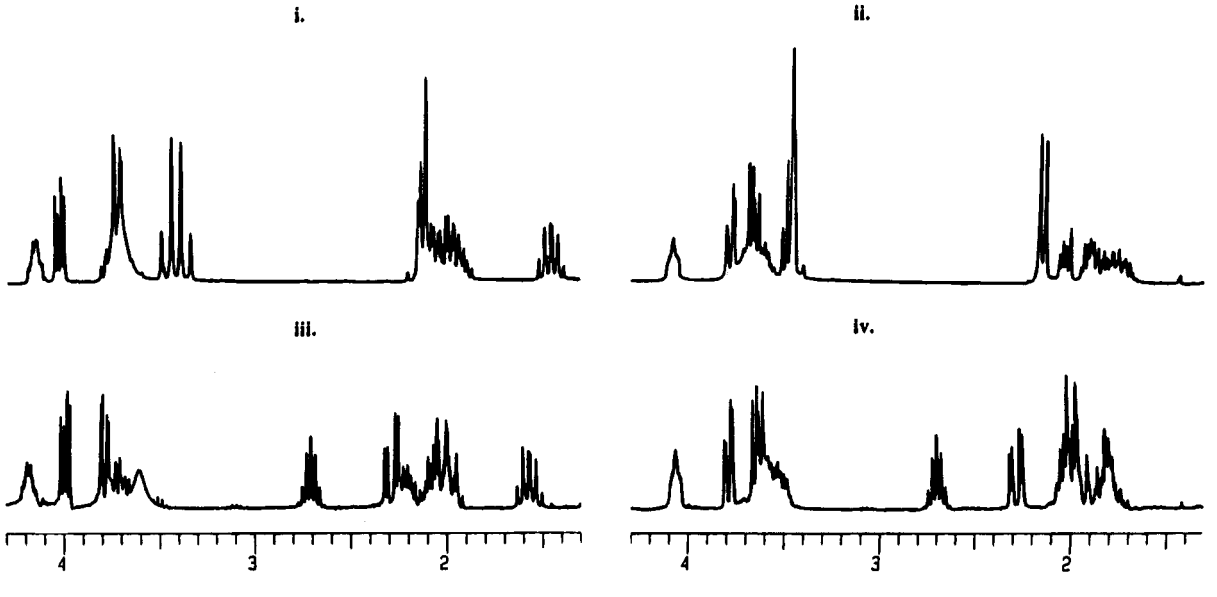


ate, two building blocks **38a** and **38b** were obtained that were isomeric at the bridgehead carbon. The 1:1 mixture of isomers was seperated at this point.

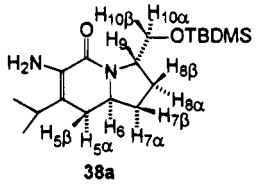
From their proton NMR data, it was obvious that **38a** and **38b** belonged to the same stereochemical "families" as did the previously discussed building blocks **29a** and **29b** (Scheme 17). The two families can be readily distinguished by several signals including the methine proton at *ca.* 4.2–4.1 ppm, the location and coupling of the A of ABX methine in the 4.0–3.8 ppm region (in isomer a this signal is at 4.0 ppm and J_{AX} is larger than J_{BX}; in isomer b this signal is at 3.8 ppm and J_{BX} is larger that J_{AX}), and the signal at *ca.* 1.5 ppm in isomer a. Using these signals, the stereochemistry of **38a** and **38b** was initially assigned in analogy to **29a** and **29b**. This stereochemical assignment was confirmed with the use of 2D-NOE experiments (Scheme 18). As earlier, the complete carbon and proton connectivities of **38a** and **38b** were established using HMQC and NOESY experiments.

As with the earlier assignment of **29a** and **29b**, the stereochemistry of the bridgehead proton in **38a** was determined by first establishing the stereochemistry of the methylene protons on C_7 and then establishing the relationship of the bridgehead proton to these protons. In this case, the stereochemistry of $H_{7\alpha}$ was assigned by noting that $H_{7\alpha}$ showed cross peaks with both of the methylene protons on C_{10}. Clearly, $H_{7\alpha}$ was cis to the (*tert*-butyldimethylsiloxy)methyl substituent. $H_{7\alpha}$ also proved to be cis to the bridgehead proton H_6. This

Scheme 17. δ 1.3–4.3 ppm Region of ^{1}H NMR ($CDCl_3$/300 MHz) Spectra of Compounds: (i) 29a; (ii) 29b; (iii) 38a; (iv) 38b

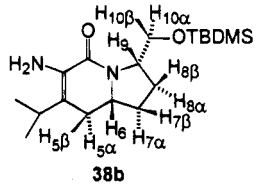


Scheme 18



38a

Signal One	Signal Two	NOE Crosspeak Volume Integral
$H_{7\alpha}$	$H_{10\alpha}$ or $H_{10\beta}$	0.22
$H_{7\alpha}$	$H_{10\alpha}$ or $H_{10\beta}$	0.23
H_6	$H_{7\alpha}$	2.30
H_6	$H_{7\beta}$	0.30



38b

Signal One	Signal Two	NOE Crosspeak Volume Integral
$H_{7\alpha}/H_{5\alpha}$	$H_{10\alpha}$ or $H_{10\beta}$	0.37
H_6	$H_{7\beta}/H_{8\beta}$	1.62

relationship could be established because of the magnitude (2.30) of the volume integral for the cross peak arising because of these two protons. This magnitude can be compared to the magnitude (0.30) of the volume integral for the cross peak arising from the trans-protons H_6 and $H_{7\beta}$. The assignment of **38b** was not as straightforward because many of the signals overlapped in this spectrum. However, a pair of key interactions were quite helpful. First, the overlapping signal for $H_{7\alpha}$ and $H_{5\alpha}$ showed a cross peak with one of the methylene protons on C_{10}. This cross peak had to arise from either a cis relationship between $H_{7\alpha}$ and the (*tert*-butyldimethylsiloxy)methyl substituent, an interaction between $H_{5\alpha}$ and the substituent, or both. Molecular models suggest that $H_{5\alpha}$ could only interact with a proton on C_{10} if the bridgehead proton C_6 was on the β-face of the molecule. Therefore, if this cross peak arises from the interaction of $C_{5\alpha}$ with the proton on C_{10}, then the stereochemistry of this isomer would be confirmed. If this cross peak was due exclusively to $H_{7\alpha}$, then a second cross peak proves valuable. The volume integral for the cross peak between H_6 and the overlapping signals for $H_{7\beta}$ and $H_{8\beta}$ had a magnitude of 1.62. Cis protons that have a 1,3-relationship across a five-membered ring typically show cross peaks with volume integrals in the range of 0.1 to 0.3. It is difficult to see why an interaction between H_6 and $H_{8\beta}$ would be any different and hence it appears that the cross peak between the H_6 and $H_{7\beta}/H_{8\beta}$ was mainly due to the interaction between H_6 and $H_{7\beta}$. The magnitude of the volume integral in this case would clearly indicate a cis-relationship between the protons and would again establish the stereochemistry of H_6 as being on the β-face of the molecule as drawn.

Building blocks **38a** and **38b** were carried on independently. Both were readily incorporated into peptide fragments using standard peptide chemistry (Scheme 19). Once the tetrapeptides were synthesized, the stereochemical assignments of the compounds were reexamined in order to make sure that the stereochemistry of the proline unit had not been lost. For both **36a** and **36b**, the complete proton and carbon connectivities were determined by HMQC-TOCSY experiments, and the stereochemistry was assigned by a combination of 2D-NOE experiments and simulation studies.[15] In both cases, the tetrapeptides were isolated as stereochemically pure compounds with the stereochemistry of the final product matching the stereochemistry of the initial building block prior to incorporation into the peptide fragment.

Initial Studies toward a Conformationally Restricted TRH Mimetic

Having successfully demonstrated that the six-membered-ring lactam building blocks could be readily incorportated into peptide fragments, we turned our attention back toward the study of conformationally restricted thyroliberin (TRH) analogs. As mentioned above, our initial targets **4** and **5** were selected because of its relationship to a series of computer-designed TRH analogs (**39** and **40**/ Scheme 20). Initially, the seven-membered ring was selected because it appeared to be the simplest to make.

However, the work described above suggested that this may not be the case and that the rearrangement reaction might allow for exploration of the six-membered-ring lactam based TRH analog series **40**. In fact, although they contained an extra methylene group building blocks **29a** and **29b** appeared to be good candidates for probing whether the six-membered-ring lactam-containing bicyclic ring skeletons could be incorporated into TRH analogs. For this reason, **29b** was converted to its corresponding TRH analog as outlined in Scheme 21. The yields for this process were not optimized due to the poor biological activity of the final product. The unrestricted homophenylalanine analog of TRH (**42**) was synthesized for comparison purposes using standard peptide coupling techniques.

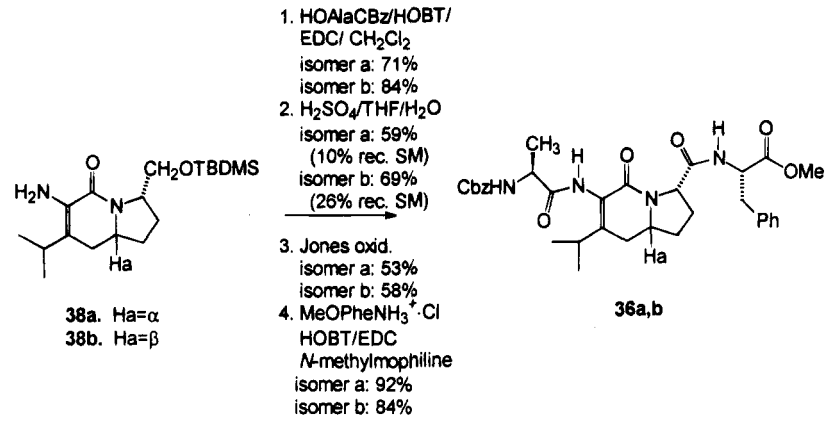
Although this work was very useful for demonstrating that the bicyclic lactam building blocks could be converted into TRH analogs, **41b** was not a useful analog for probing the effect of the lactam ring on TRH binding. Both the restricted analog **41b** and the unrestricted analog **42** showed very little affinity for the TRH endocrine receptor site. In both cases, the binding constant for the analog was about three orders of magnitude less than the binding constant obtained for TRH.[16] The affinities for both molecules were low enough to preclude any useful comparison between the two compounds. In addition, the p-Glu-Phe-Pro-NH_2 TRH analog is known to bind to the endocrine receptor with the same order of magnitude as TRH.[17] Clearly, the extra methylene added to analog **42** interfered with binding. Again, no conclusions could be reached with respect to the how the six-membered-ring lactam in analog **41b** influenced binding because it also contained the extra methylene group. To understand the role of the lactam in binding a lactam based TRH analog without the extra methylene will be required.

Conclusions

A rearrangement reaction discovered during an attempt to synthesize seven-membered-ring lactam based peptide building blocks has led to a new route for

(15) Unpublished results with Wenhao Li and Dr. Jeff Kao.
(16) Unpublished results with Professor Marvin Gershengorn and Dr. Jeffrey Perlman.
(17) For a nice summary of TRH analog binding information see Marshall, G. R.; Gorin, F. A.; Moore, M. L. In *Annual Reports in Medicinal Chemistry*; Clarke, F. H., Ed., Academic Press: New York, 1978; Vol. 13, p 227 and references therein.

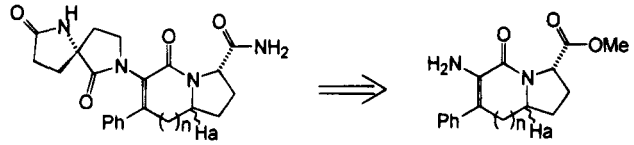
Scheme 19



38a. Ha=α
38b. Ha=β

36a,b

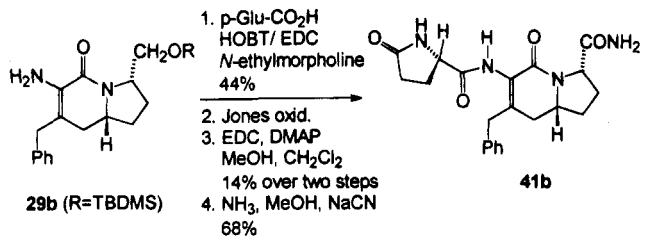
Scheme 20



39. n=2
40. n=1

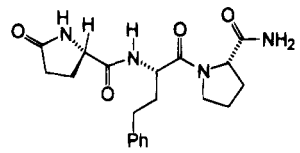
4. n=2
5. n=1

Scheme 21



29b (R=TBDMS)

41b



42

constructing bicyclic ring skeletons containing six-membered-ring lactams. The bicyclic lactams generated can be converted into peptide building blocks and incorporated into peptide fragments as conformationally restricted X-Pro units. Although the initial building blocks generated were not ideal for probing the effect of six-membered-ring lactam based peptide mimetics on binding to the TRH endocrine receptor site, the synthetic route developed was shown to be compatible with the construction of a conformationally restricted amino acid with a branched side chain and should be readily applicable to the synthesis of more effective chemical probes for studying TRH–receptor binding. Studies along these lines are currently underway and will be reported in due course.

Experimental Section[18]

3-Phenyl-4-pentenoic Acid. Cinnamyl alcohol (13.46 g, 100 mmol), triethyl orthoacetate (81.15 g, 500 mmol), and propionic acid (441 mg, 6.0 mmol) were added to a flame-dried 250 mL round-bottom flask. The flask was equipped with a Dean–Stark trap and a condenser and the reaction brought to reflux. After approximately 85 mL of solution was removed from the reaction, the reflux was halted and MeOH (100 mL) and KOH (11.27 g, 200 mmol) were added to the mixture. The reaction was refluxed for another 5 h. The MeOH was then removed under reduced pressure and the crude oil partitioned between an aqueous solution of saturated $NaHCO_3$ and Et_2O. The aqueous layers were combined, acidified to a pH of 1, and then extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude oil was then distilled to afford 14.167 g (80%) of the desired acid product. The spectral data for the acid were as follows: ^1H NMR ($CDCl_3$/300 MHz) δ 11.6 (br s, 1H), 7.34–7.20 (m, 5H), 5.98 (ddd, 1H, J = 17.2, 10.0, 6.8 Hz), 5.14–5.03 (m, 2H), 3.86 (app q, 1H, J = 7.3 Hz), 2.94–2.69 (m, 2H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 179.0, 142.7, 140.4, 129.1, 128.0, 127.3, 115.4, 45.3, 40.1; IR (neat/NaCl) 3550–2100 br, 1705, 1640, 1494, 1453, 1417, 1291, 1205, 992, 923, 758, 700 cm^{-1}; GCMS (PCI) *m/e* (rel intensity): 177 (M + 1, 34), 159 (35), 136 (13), 135 (70), 132 (20), 131 (100), 117 (60), 99 (16), 91 (20), 61 (24); HRMS (EI) *m/e* calcd for $C_{11}H_{12}O_2$ 176.0837; found 176.0825; mp = 45.1–46.0 °C.

(2*S*)-2-(Hydroxymethyl)-1-(3-phenyl-4-pentenoyl)pyrrolidine (19). To a mixture of the acid generated above (10.519 g, 59.7 mmol) in 120 mL of CH_2Cl_2 were added HOBt (11.290 g, 83.6 mmol) and L-prolinol (6.642 g, 65.7 mmol). The mixture was stirred at 0 °C for 5 min and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) (14.835 g, 77.6 mmol) added. The resulting mixture was allowed to warm to rt and stirred at rt overnight. The reaction was then poured into a separatory funnel and washed with saturated $NaHCO_3$, 10% citric acid, and an aqueous saturated NaCl solution. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was then chromatographed through ca. 600 g of silica gel using a 4% MeOH in Et_2O solution as eluant to afford 11.721 g (76%) of compound **19** as a colorless oil. A mixture of diastereomers was obtained. The spectral data for the mixture were as follows: ^1H NMR (300 MHz/$CDCl_3$) δ 7.34–7.20 (m, 5H), 6.08 (ddd, 1H, J = 17.0, 10.5, 6.5 Hz), 5.13 (d, 1H, J = 7.5 Hz), 5.08 (d, 1H, J = 13.8 Hz), 4.16–4.10 (m, 1H), 3.98 (app q, J = 6.5 Hz), 3.64–3.24 (m, 4H), 3.29–3.24 (m, 0.5H), 3.08 (dt, 0.5H, J_d = 10.1 Hz, J_t = 7.0 Hz), 2.79–2.62 (m, 2H), 1.99–1.48 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 173.3, 173.2, 143.3, 143.1, 140.9, 140.7, 129.0, 128.2, 128.1, 127.2, 115.3, 115.2, 67.2, 67.1, 61.2, 48.4, 46.0, 45.7, 41.0, 40.8, 28.2, 24.4, 24.3; IR (neat/NaCl) 3400 br, 3082, 3061, 3028, 2949, 2927, 2904, 2882, 1652, 1493, 1467, 1192, 1076, 1053, 1002, 996, 917, 760, 706, 676 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 300 (M + 41, 5), 289 (M + 30, 4), 288 (M + 29, 14), 262 (M + 3, 4), 261 (M + 2, 29), 260 (M + 1, 100), 259 (M, 4), 258 (M − 1, 5), 242 (6), 228 (7); HRMS (EI) *m/e* calcd for $C_{16}H_{21}O_2N$ 259.1572; found, 259.1598. Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.00; H, 8.09; N, 5.26.

(2S)-2-[(Benzyloxy)methyl]-1-(3-phenyl-4-pentenoyl)-pyrrolidine (17). A solution of compound **19** (11.064 g, 42.7 mmol) in 50 mL of THF was added dropwise to a suspension of NaH (2.563 g of a 60% mixture with mineral oil, 64.1 mmol) in 30 mL of THF at 0 °C. The mixture was allowed to warm

(18) For a general experimental section please see reference 6k.

to rt, stirred for 30 min, cooled to 0 °C, and treated with benzyl bromide (8.037 g, 47.0 mmol). The reaction was allowed to warm to rt, stirred overnight, and then quenched by adding an aqueous, saturated NaCl solution. The emulsion was transferred to a separatory funnel, diluted with Et_2O, and washed with water. The aqueous layers were combined and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was then chromatographed through ca. 500 g of silica gel using a 20% hexane in Et_2O solution as eluant to afford 12.95 g (87%) of compound **17** as a colorless oil. The spectral data for the mixture of diastereomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.39–7.13 (m, 10H), 6.12–5.95 (m, 1H), 5.10–5.01 (m, 2H), 4.54–4.36 (m, 2H), 4.32–4.20 (m, 1H), 4.09–3.95 (m, 1H), 3.72–3.09 (m, 4H), 2.79–2.57 (m, 2H), 1.20–1.65 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 170.8, 170.1, 143.1, 140.9, 140.8, 140.7, 138.6, 137.9, 128.4, 128.3, 127.8, 127.6, 127.5, 126.5, 126.4, 114.5, 73.1, 72.9, 71.3, 70.9, 69.9, 69.6, 56.8, 56.7, 56.2, 47.1, 45.5, 45.2, 45.1,45.0, 40.4, 39.9, 28.4, 28.1, 27.1, 23.7, 21.05; IR (neat/NaCl) 3070, 3062, 3029, 2974, 2875, 1718, 1636, 1495, 1452, 1420, 1395, 1384, 1251, 1197, 1182, 1102, 1032, 1001, 914, 739, 700, 672 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 351 (M + 2, 8), 350 (M + 1, 21), 228 (6), 128 (7), 119 (10), 117 (16), 115 (6), 102 (13), 100 (6), 92 (9), 91 (55), 71 (15), 70 (100); HRMS (EI) *m/e* calcd for $C_{23}H_{27}O_2N$ 349.2042; found 349.2048. Anal. Calcd for $C_{23}H_{27}O_2N$: C, 79.04; H, 7.79; N, 4.01. Found: C, 79.26; H, 7.98; N, 4.01.

(2*S*)-2-[(Benzyloxy)methyl]-5-methoxy-1-(3-phenyl-4-pentenoyl)pyrrolidine (20). An oven-dried three-neck flask was charged with compound **17** (6.703 g, 2.01 mmol), MeOH (50 mL), and tetraethylammonium tosylate (0.452 g, 1.50 mmol) and equipped with a carbon anode, a platinum wire cathode, and a nitrogen inlet. The mixture was degassed by sonication while a slow stream of nitrogen was passed through the solution for 5 min. The mixture was then electrolyzed at a constant current of 26.8 mA until 2.5 F/mol had been passed. The MeOH was then removed under reduced pressure and the crude oil chromatographed through ca. 100 g of silica gel using a gradient elution from 70% ether/hexane to ether. The column afforded 4.360 g (60%) of the desired methoxylated amide **20** as a mixture of diastereomers along with 2.279 g (34%) of the recovered starting material **17**. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.36–7.15 (m, 10H), 6.13–5.94 (m, 1H), 5.14–4.97 (m, 2H), 4.71–4.32 (m, 3H), 4.18–3.75 (m, 2H), 3.60–3.15 (m, 5H), 2.95–2.63 (m, 2H), 2.14–1.71 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 172.0, 171.9, 143.5, 143.3, 143.1, 141.1, 140.9, 140.7, 140.5, 138.7, 138.0, 128.9, 128.7, 128.6, 128.4, 127.9, 127.8, 127.7, 127.6, 126.8, 126.6, 126.5, 114.9, 114.6, 114.5, 89.5, 89.4, 89.3, 87.6, 75.0, 74.5, 73.3, 73.2, 73.0, 71.7, 71.6, 69.8, 69.3, 57.0, 56.8, 56.7, 56.6, 56.4, 56.3, 55.4, 53.7, 53.6, 46.5, 45.3, 45.1, 45.0, 40.0, 39.9, 39.8, 39.3, 30.5, 30.3, 30.0, 29.4, 29.1, 28.8, 28.6, 26.9, 26.3, 25.6, 24.6, 24.3; IR (neat/NaCl) 3029, 2980, 2939, 1665, 1653, 1496, 1457, 1442, 1404, 1363, 1198, 1072, 1101, 914, 737, 700, 663 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 380 (M + 1, 2), 348 (5), 191 (22), 190 (100), 126 (5), 121 (5), 117 (13), 115 (5), 101 (9), 100 (59), 98 (9), 92 (5), 91 (30), 68 (10); HRMS (EI) *m/e* calcd for $C_{24}H_{29}O_3N$ 379.2147; found 379.2147.

(9*S*)-1-Aza-4-(chlorobenzyl)-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]nonane (22). To a −78 °C solution of the methoxylated amide **20** (5.893 g, 15.5 mmol) in 40 mL of CH_2Cl_2 was added 38.9 mL of a 1 M $TiCl_4$ in CH_2Cl_2 solution. The mixture was allowed to warm to rt and stirred overnight. The reaction was then quenched by the addition of a 30% solution of Rochelle's salt in water. The reaction mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted 10 times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was then chromatographed through 10 g of silica gel using a 10% solution of MeOH in ether as the eluant to afford 4.107 g (90%) of the cyclized compound **22** as a yellow oil. The spectral data for the mixture of diastereoisomers obtained were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.41–7.32 (m, 5H), 4.75–4.62 (four overlapping d, 1H, J = 3.9, 3.9, 4.5, 4.2 Hz), 4.25–4.09 (m, 1H), 3.73–3.62 (m, 1.5H), 3.55–3.37 (m, 1.5H), 2.30–1.07 (m, 10H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.0, 170.9, 170.6, 139.3, 139.2, 139.1, 129.0, 128.9, 128.8, 127.5, 127.4, 67.9, 67.5, 67.3, 67.0, 66.7, 65.8, 61.2, 60.9, 60.6, 60.5, 59.0, 58.9, 41.8, 41.7, 41.3, 41.2, 35.7, 35.5, 35.3, 34.9, 32.8, 32.5, 32.2, 31.7, 31.0, 29.8, 29.5, 29.2, 29.1, 27.2, 26.0, 22.4, 15.0, 13.9; IR (neat/NaCl) 3377 br, 3059, 3032, 2942, 2872, 1617, 1457, 1411, 1367, 1327, 1239, 1198, 1051, 834, 731, 701 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 322 (M + 29, 13), 296 (M + 3, 33), 295 (M + 2, 19), 294 (M + 1, 100), 262 (8), 260 (8), 259 (15), 258 (72), 100 (84), 59 (12), 57 (72), 56 (7); HRMS (EI) *m/e* calcd for $C_{16}H_{20}O_2NCl$ 293.1183; found 275.1108 (M − H_2O). Anal. Calcd for $C_{16}H_{20}O_2NCl$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.78; H, 7.01; N, 4.81.

3-Methyl-4-pentenoic Acid. A 100 mL single-neck round-bottom flask equipped with a reflux condenser was charged with 2.0 g (28 mmol) of crotyl alcohol, 15.7 g (97.0 mmol) of triethyl orthoacetate, and 0.12 g (1.7 mmol) of propionic acid. Boiling chips were added, and then the mixture was heated to reflux for 3 h. A Dean–Stark trap was then attached and the mixture heated until no more ethanol could be removed. After 4.5 h, the reaction was cooled to room temperature and 3.11 g (55.4 mmol) of potassium hydroxide and 30 mL of methanol were added. This solution was heated to reflux for 18 h. The reaction was warmed to room temperature and concentrated *in vacuo*. The resulting residue was taken up in diethyl ether and extracted three times with a saturated solution of sodium bicarbonate. The aqueous extracts were combined, acidified with 6 N HCl, and extracted five times with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, and concentrated to an oil. The crude product was distilled to afford 2.12 g, 67% yield, of the desired carboxylic acid as a clear colorless oil. The spectral data were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 11.6 (br s, 1H), 5.78 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.03 (dd, J = 17.2, 10.4 Hz, 2H), 2.69 (m, 1H), 2.37 (two dd, J = 15.1, 7.6 Hz, 2H), 1.09 (d, J = 6.8 Hz, 3H); IR (neat/NaCl) 2974, 1708, 1413, 1293, 1201, 913 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 116 (M + 2, 13), 115 (M + 1, 100), 114 (M + , 5), 97 (62), 73 (20); HRMS (EI) *m/e* calcd for $C_6H_{10}O_2$ 114.0681; found 114.0686.

1-(3-Methyl-4-pentenoyl)-2-(hydroxymethyl)pyrrolidine. A 100 mL single-neck round-bottom flask was charged with 100 mg (0.88 mmol) of 3-methyl-4-pentenoic acid, 0.103 mg (1.05 mmol) of (*S*)-(+)-2-pyrrolidinemethanol, 166 mg (1.23 mmol) of *N*-hydroxybenzotriazole, 0.13 mL (1.05 mmol) of *N*-ethylmorpholine, and 5 mL of dichloromethane. This mixture was cooled to ca. 0 °C in an ice bath and 201 mg (1.05 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride added. The mixture was stirred for three days. The reaction was quenched with the addition of a saturated solution of sodium bicarbonate. The layers were separated, and the organic layer was washed three times with a saturated solution of sodium bicarbonate, three times with a 5% solution of citric acid, and one time with a saturated solution of sodium chloride. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude product mixture was distilled at 150 °C and 0.1 mmHg to afford 124 mg (71%) of the pure amide as a clear, colorless oil. A 1:1 mixture of two stereoisomers was obtained. The spectral data for the mixture of diastereomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.82 (ddd with fine coupling, J = 16.5, 10.4, 7.1 Hz, 1H), 5.04 (dm, J = 17.3 Hz, 1H), 4.97 (d, J = 10.4 Hz, 1H), 4.23 (m, 1H), 3.56 (m, 4H), 2.31 (m, 2H), 1.92 (m, 3H), 1.61 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 173.2, 142.8, 142.6, 113.1, 113.0, 67.3, 67.2, 60.9, 48.2, 41.6, 39.8, 34.2, 34.1, 28.2, 24.3, 19.6, 19.5; IR (neat/NaCl) 3388, 3081, 2962, 2875, 1612, 1431, 1332, 1194, 1050, 912 cm^{-1}; bp = 150 °C at 0.1 mm; LRMS (FAB) *m/e* (rel intensity) 198 (M + 1, 100), 199 (M + 2, 23); HRMS (FAB) *m/e* calcd for $C_{11}H_{20}NO_2$ 198.1494; found 198.1502.

1-(3-Methyl-4-pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine. A 100 mL single-neck round-bottom flask was charged with 484 mg (16.8 mmol) of an 80% dispersion of sodium hydride in oil. The powder was washed three times with hexanes to remove the oil and then 15 mL of tetrahydrofuran added. This slurry was cooled to 0 °C and then 2.21 g (11.2 mmol) of 1-(3-methyl-4-pentenoyl)-2-(hydroxymethyl)pyrrolidine in 10 mL of tetrahydrofuran added. After 20 min, 2.30 g (13.4 mmol) of benzyl bromide was added. After an additional

15 min at 0 °C, the mixture was warmed to room temperature and allowed to stir for two days. The reaction was quenched with the addition of a saturated solution of sodium chloride, the layers were separated, and the organic layer was washed three times with a saturated solution of sodium chloride. The aqueous washings were back extracted two times with ether. The organic fractions were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product mixture was distilled at 180 °C and 0.2 mmHg to afford 2.31 g (72%) of the desired product as a clear, colorless oil. The spectral data for the mixture of diastereomeric products (two diastereomers plus amide rotomers) were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.33 (m, 5H), 5.81 (m, 1H), 4.99 (m, 2H), 4.55 (A of AB, J = 12.0 Hz, 1H), 4.50 (B of AB, J = 12.0 Hz, 1H), 4.34 (m, 0.66 H), 4.06 (m, 0.33 H), 3.68 and 3.65 (two d, J = 3.2, 0.5H), 3.49 (m, 3.5H), 2.79 (m, 1H), 2.27 (m, 2H), 1.96 (m, 4H), 1.08, 1.07, 1.03, and 1.02 (four d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 172.3, 170.6, 143.2, 143.1, 128.4, 128.2, 127.7, 127.5, 127.4, 112.8, 112.7, 112.6, 106.0, 73.2, 73.0, 71.1, 70.1, 70.0, 57.0, 56.9, 56.3, 47.4, 45.4, 41.6, 41.5, 41.0, 34.4, 34.0, 33.9, 28.8, 28.7, 27.5, 24.1, 21.8, 19.6, 19.5; IR (neat/NaCl) 2960, 2873, 1642, 1450, 1419, 1103 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 289 (M + 2, 44), 288 (M + 1, 100), 196 (15), 180 (42), 119 (40), 91(61); HRMS (EI) *m/e* calcd for $C_{18}H_{25}NO_2$ 287.1885; found 287.1884.

5-Methoxy-1-(3-methyl-4-pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine (23a). An oven-dried vial equipped with a magnetic stir bar and a rubber stopper with an N_2 inlet, a carbon rod anode, and a platinum wire cathode was charged with 1.30 g (4.52 mmol) of 1-(3-methyl-4-pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine, 82 mg (0.27 mmol) of tetraethylammonium toluenesulfonic acid, and 9 mL of anhydrous methanol. The solution was degassed by sonication under a slow stream of nitrogen for 10 min. The reaction was then electrolyzed at a constant current of 53.6 mA until 981.2 C (2.25 F/mol) had been passed through the solution. The reaction mixture was then concentrated *in vacuo* and chromatographed through 40 g of silica gel that was slurry packed with 2:1 ether/hexanes. The elution was done with 2:1 ether/hexanes to afford 685 mg (48%) of the methoxylated amide product along with 377 mg (30%) of the recovered starting material. The spectral data for the methoxylated products were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.32 (m, 5H), 5.81 (m, 0.8H), 5.65 (m, 0.2H), 4.99 (m, 2.5H), 4.54 (m, 2H), 4.37 (m, 0.6H), 4.12 (m, 0.2H), 3.92 (m, 0.2H), 3.49 (m, 2.5H), 3.29 and 3.23 (two s, 3H), 2.81 (m, 1H), 2.39 (m, 2H), 1.96 (m, 4H), 1.09 (m, 3H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 172.3, 172.2, 171.6, 143.3, 143.1, 143.0, 142.9, 138.4, 138.3,128.3,128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 127.2, 113.0, 112.8, 112.7, 112.5,89.5, 89.4, 87.5, 87.4, 74.6, 73.2, 73.0, 71.7, 69.8, 69.5, 56.8, 56.6, 56.3, 55.5, 53.9, 53.8, 41.0, 40.9, 40.8, 40.4, 34.3, 34.1, 34.0, 33.9, 33.8, 33.7, 30.7, 30.5, 28.9, 28.8, 27.0, 26.9, 25.9, 24.6, 19.7, 19.5, 19.4, 19.3; IR (neat/NaCl) 3433, 2967, 2870, 1653, 1405, 1193, 1083, 915, 740, 697 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 318 (M + 1, 2), 287 (4), 286 (16), 218 (4), 191 (24), 190 (100), 126 (4), 119 (6), 100 (4), 91 (5).

1-Aza-4-(1-chloroethyl)-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]nonane (24a). A 100 mL single-neck round-bottom flask was charged with 680 mg (2.14 mmol) of 5-methoxy-1-(3-methyl-4-pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine and 10 mL of dichloromethane. The reaction was cooled to −78 °C and 5.36 mL (5.36 mmol) of a 1.0 M titanium tetrachloride in dichloromethane solution added in a dropwise fashion. After 15 min, the reaction was warmed to room temperature and stirred for 18 h. The reaction was quenched with the addition of a saturated solution of sodium bicarbonate. The layers were separated, and the organic layer was washed two times with a saturated solution of sodium bicarbonate and one time with a saturated solution of sodium chloride. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo*. The crude product was distilled at 160 °C and 0.1 mmHg to afford 410 mg (82%) of the cyclized product. The spectral data for the cyclized product were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.91 (br s, 1H), 4.45−3.48 (m, 5H), 2.72−1.05 (m, 11H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 67.9, 67.8, 67.4, 65.8, 61.4, 61.3, 61.1, 60.7, 60.4, 59.4, 59.4, 59.1, 59.8, 58.9, 57.2, 45.8, 43.9, 40.8, 40.7, 40.1, 35.3, 35.1, 33.2, 33.0, 32.98, 32.92, 32.6, 32.4, 32.2, 32.0, 31.4, 31.3, 31.2, 31.1, 31.0, 27.3, 27.3, 26.9, 26.2, 25.8, 22.4, 22.3, 11.2; IR (neat/NaCl) 3360, 2966, 2931, 2875, 1616, 1447, 1327, 1047, 921, 731 cm^{-1}; LRMS (PCI) *m/e* (rel intensity): 232 (M + 1, 100), 196 (M − Cl, 56), 214 (M − OH, 10), 100 (28). Due to the complexity of the spectral data, the number of isomers was reduced by dechlorination before complete characterization data was obtained.

1-Aza-4-ethyl-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]-nonane. A 50 mL single-neck round-bottom flask was charged with approximately 1 g of a 50% mixture of Raney nickel in water. The mixture was washed several times with methanol in order to remove the water and then 5 mL of methanol added followed by 199 mg (3.54 mmol) of potassium hydroxide. A solution of 410 mg (1.78 mmol) of 1-aza-4-(1-chloroethyl)-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]nonane in 5 mL of methanol was then added. The resulting mixture was stirred under a balloon of hydrogen for two days. Since starting material remained by TLC at this point, an additional 200 mg of Raney nickel was added and the mixture stirred an additional 24 h. When the reaction was complete, the catalyst was removed by filtration through a plug of Celite and washed with methanol. The filtrate was concentrated *in vacuo* and the resulting residue taken up in dichloromethane, washed three times with a 5% solution of citric acid, and washed one time with a saturated solution of sodium chloride. The organic layer was then dried over magnesium sulfate and concentrated *in vacuo* to afford 257 mg (73%) of the dechlorinated product. No further purification was needed. A 1:1 mixture of two diastereomers was obtained. The spectral data for the mixture of diastereomers were as follows: ^{1}H NMR (500 MHz/$CDCl_3$) δ 5.20 (br s, 1H), 4.23 (app q, J = 7.8 Hz, 0.5 H), 4.16 (app t, J = 7.3, 0.5 H), 3.58 (m, 3H), 2.61 (app d, J = 5.4, 0.25H), 2.57 (app t, J = 6.8, 0.5H), 2.52 (app d, J = 6.4, 0.25H), 2.03 (m, 4H), 1.73 (m, 1H), 1.38 (m, 3H), 1.03 (m, 1H), 0.95, 0.93, and 0.92 (three d, J = 2.9, 3H); ^{13}C NMR (125 MHz/$CDCl_3$) δ 171.6, 171.5, 68.0, 67.6, 61.3, 61.2, 61.0, 59.6, 38.0, 37.8, 35.3, 35.2, 35.1, 34.5, 32.6, 31.3, 29.1, 28.8, 27.4, 26.3, 11.2, 11.1; IR (neat/NaCl) 3380, 2954, 2915, 2870, 1620, 1450, 1330 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 199 (M + 2, 99.9), 198 (M + 1, 100), 197 (M$^+$, 37), 196 (73), 182 (18), 180 (62), 166 (59); HRMS (EI) *m/e* calcd for $C_{11}H_{19}NO_2$ 197.1416; found 197.1417. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.71; N, 7.10. Found: C, 66.64; H, 9.72; N, 7.08. Bp = 145 °C at 0.25 mmHg. Attached proton test and HMQC-TOCSY data are included in the supporting information.

***N*-(4-Pentenoyl)-2-(hydroxymethyl)pyrrolidine.** A 500 mL single-neck round-bottom flask was charged with 200 mL of dichloromethane, 10.2 mL (100 mmol) of pentenoic acid, 11.8 mL (120 mmol) of (*S*)-(+)-2-pyrrolidinemethanol, 18.9 g (140 mmol) of hydroxybenzotriazole, and 15.3 mL (120 mmol) of *N*-ethylmorpholine. This solution was cooled to 0 °C and 28.8 g (140 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide. After 15 min, the reaction was warmed to room temperature and stirred for three days. The reaction was then quenched with the addition of saturated sodium bicarbonate. The layers were separated, and the organic layer was washed three times with saturated sodium bicarbonate and three times with 5% citric acid, dried over magnesium sulfate, and concentrated *in vacuo*. The reaction afforded 16.91 g of the crude product which was carried on without further purification. The spectral data were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.88 (m,1H), 5.03 (dd, J = 18, 12 Hz, 2H), 4.43 (br s, 1H), 4.21 (m, 1H), 3.69−3.42 (m, 4 H), 2.44 (m, 1H), 2.41 (s, 3H), 2.10−1.81 (m, 4H), 1.63 (m, 1 H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 173.4, 137.0, 115.2, 66.9, 60.9, 47.9, 34.1, 28.7, 28.0, 24.2; IR (neat/NaCl) 3370, 3070, 2969, 2877, 1625, 1430, 1193, 1062, 908 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 185 (M + 2, 60), 184 (M + 1, 100), 183 (M$^+$, 15), 182 (M − 1, 9), 166 (25), 103 (12), 102 (66), 84 (14), 70 (11); HRMS (EI) *m/e* calcd for $C_{10}H_{17}NO_2$ 183.1259; found 183.1239. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.35; N, 7.64. Found: C, 65.04; H, 9.33; N, 7.56.

***N*-(4-Pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine.** A 500 mL single-neck round-bottom flask was charged with approximately 2 g of NaH (80% in oil). The solid was washed several times with hexanes, 150 mL of tetrahydrofuran was added, and the mixture cooled to 0 °C. To this mixture was

added slowly 16.91 g (92 mmol) of *N*-(4-pentenoyl)-2-(hydroxymethyl)pyrrolidine in 50 mL of tetrahydrofuran. The mixture was stirred for 30 min at 0 °C, and then 130.1 mL (110 mmol) of benzyl bromide was added slowly. After 15 min, the reaction was warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated sodium chloride. Diethyl ether (100 mL) was added, and the layers were separated. The organic layer was washed three times with saturated sodium chloride, dried over magnesium sulfate, and concentrated *in vacuo*. Vacuum distillation (170 °C at 0.2 mmHg) afforded 21.05 g (77% over two steps) of the desired product. The spectra data were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.31 (m, 5H), 5.58 (m, 1H), 5.03 (m, 2H), 4.52 (A of AB, J = 15 Hz, 1H), 4.48 (B of AB, J = 15 Hz, 1H), 4.30 (m, 0.75H), 4.05 (m, 0.25H), 3.49 (m, 4H) 2.38 (m, 4H), 1.95 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.0, 138.5, 137.6, 128.4, 128.2, 127.7, 127.5, 127.4, 114.9, 73.3, 73.0, 71.2, 70.0, 57.0, 56.4, 47.2, 45.5, 34.1, 33.5, 29.4, 28.8, 27.5, 24.1, 21.8; IR (neat/NaCl) 3053, 3021, 2966, 2863, 1640, 1418, 1102, 747 cm^{-1}; GCMS *m/e* (rel intensity) 275 (M + 2, 18), 274 (M + 1, 79), 182 (14), 166 (39), 152 (11), 119 (33), 102 (10), 100 (12), 92 (10), 91 (100), 70 (18); HRMS (EI) *m/e* calcd for $C_{17}H_{23}NO_2$ 273.1729; found 273.1725. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.42: N, 5.13. Found: C, 73.60; H, 8.54; N, 5.98.

5-Methoxy-1-(4-pentenoyl)-2-[(benyloxy)methyl]pyrrolidine (23b). A 250 mL three neck round-bottom flask was fitted with a Pt wire cathode, a carbon rod anode, and a septum. A syringe needle was pushed through the septum and used as a nitrogen inlet. The flask was charged with 21.05 g (77 mmol, 0.5 M) of *N*-(4-pentenoyl)-2-[(benzyloxy)methyl]-pyrrolidine, 150 mL of anhydrous methanol, and 1.39 g (4.62 mmol, 0.03 M) of tetraethylammonium tosylate. The solution was degassed by sonication under a slow stream of nitrogen for 10 min. The reaction was then electrolyzed at a constant current of 42.2 mA. After 2.3 F/mol had been passed, the reaction mixture was transferred to a round-bottom flask and concentrated *in vacuo*. The viscous liquid was immediately chromatographed through a silica gel column which was slurry packed with a 2:1 ether in hexanes solution. Elution with the same solvent mixture afforded 14.39 g (62%) of the desired product along with 4.89 g (23%) of recovered starting material. The spectral data for the mixture of stereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.36 (m, 5H), 5.85 (m, 0.8H), 5.63 (m, 0.2H), 5.00 (m, 2H), 4.51 (m, 2H) 4.32 (m, 0.66H), 4.12 (m, 0.33H), 3.91 (m, 0.1H), 3.51 (m, 2.9H), 3.29 and 3.26 (two s, 3H), 2.45 (m, 4H), 1.99 (m, 4H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 138.5, 137.7, 137.5, 128.5, 128.4, 128.3, 128.2, 127.7, 127.69, 127.6, 127.5, 127.4, 115.2, 115.0, 114.9, 89.6, 89.6, 87.7, 74.8, 73.4, 73.1, 71.8, 69.8, 57.0, 56.7, 56.5, 55.6, 54.0, 33.6, 33.5, 33.0, 30.7, 30.5, 29.0, 28.96, 27.0, 25.9, 24.7; IR (neat/NaCl) 2973, 2943, 1663, 1454, 1437, 1404, 1364, 1317, 1200, 1088, 913 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 304 (M + 1, 15), 273 (20), 272 (70), 191 (70), 190 (100), 189 (13), 164 (13), 119 (28), 100 (22), 92 (14), 91(77); HRMS (EI) *m/e* calcd for $C_{18}H_{25}NO_3$ 303.1834; found 303.1851; bp = 165 °C at 0.025 mm.

1-Aza-5-chloro-10-(hydroxymethyl)-2-oxobicyclo[5.3.0]-decane (25b). A 500 mL single-neck round-bottom flask was charged with 8.50 g (28.0 mmol) of 5-methoxy-1-(4-pentenoyl)-2-[(benzyloxy)methyl]pyrrolidine and 140 mL of dichloromethane. The solution was cooled to −78 °C and 70.0 mL (70.0 mmol) of a 1.0 M titanium(IV) chloride in dichloromethane solution added slowly. After 30 min, the reaction was warmed to room temperature and stirred for 40 h. The reaction was quenched with a dropwise addition of a 30% (w/w) sodium potassium tartrate solution. Once the reaction was quenched, the mixture was transferred to a 1 L Erlenmeyer flask and an additional 300 mL of 30% sodium potassium tartrate solution added. The resulting emulsion was stirred for 3 h until the layers had separated. The mixture was transferred to a separatory funnel and the aqueous layer extracted five times with dichloromethane. The extracts were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was distilled by Kugelrohr (190 °C at 0.1 mmHg) to afford 4.83 g (79%) of the desired product. The spectral data was as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.62 (m, 0.5H), 4.36 (m, 2H), 4.03 (m, 0.6H), 3.88 (m, 0.4H), 3.69 (m, 2.5H), 3.12 (m, 0.5H), 2.63 (m, 0.5H), 2.07 (m, 9H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 66.9, 66.6, 66.5, 66.4, 62.0, 61.9, 60.1, 59.8, 59.2, 57.6, 57.5, 53.4, 53.3, 46.1, 45.7, 43.5, 42.8, 35.4, 35.2, 33.1, 33.0, 32.7, 32.4, 32.3, 31.9, 31.6, 31.0, 30.9, 26.6, 26.4; IR (neat/NaCl) 3287, 2912, 2718, 1612, 1456, 1375, 1031, 1006, 750 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 246 (4), 220 (29) , 219 (M + 2, 9), 218 (M + 1, 100), 200 (4), 186 (10), 183 (3), 182 (45), 100 (75). The compound was dechlorinated before final characterization.

1-Aza-10-(hydroxymethyl)-2-oxobicyclo[5.3.0]decane. A 250 mL single-neck round-bottom flask was charged with approximately 4 g of a 50% Raney nickel in water mixture. The solid was washed several times with methanol to remove the water, and then 80 mL of methanol and 3.40 g (60.6 mmol) of potassium hydroxide were added. The mixture was stirred for a few minutes to dissolve the potassium hydroxide, and then 6.60 g (30.3 mmol) of 1-aza-4-chloro-10-(hydroxymethyl)-2-oxobicyclo[5.3.0]decane in 20 mL of methanol was added. The resulting mixture was stirred under a hydrogen balloon for 48 h. An additional 2 g of washed Raney nickel was added and the reaction continued for an additional 24 h. The reaction mixture was filtered through a plug of Celite and washed with methanol to remove the catalyst. The filtrate was then concentrated *in vacuo*, and the crude product was chromatographed through a silica gel column that was slurry packed with diethyl ether. Elution with ether followed by a 10% methanol in ether solution afforded 4.06 g (73%) of the desired product as a mixture of diastereomers. The spectral data for the diastereomeric mixture were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.32 (m, 1H), 4.05 (m, 0.5H), 3.90 (m, 0.5H), 3.70 (m, 3H), 2.49 (m, 2.5H), 2.17 (m, 1.5H), 1.72 (m, 8H); ^{13}C (75 MHz/$CDCl_3$) δ 67.5, 67.2, 62.1, 61.9, 60.4, 60.3, 38.3, 37.9, 36,3, 35.5, 33.0, 32.7, 29.5, 29.4, 26.6, 26.5, 23.1, 22.9; IR (neat/NaCl) 3330, 2931, 2862, 1612, 1456, 1375, 1262, 1212, 1175, 1050 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 212 (9), 185 (M + 2, 22), 184 (M + 1, 100), 183 (M, 5), 182 (7), 167 (3), 166 (15), 152 (11); HRMS FAB calcd for $C_{10}H_{18}NO_2$ (M + 1) 184.1337; found 184.1335; bp = 175 °C at 0.1 mm.

(9*S*)-1-Aza-4-benzyl-9-(hydroxymethyl)-2-oxobicyclo-[4.3.0]nonane. To a solution of the cyclized compound **22** (1.696 g, 5.77 mmol) in 10 mL of MeOH was added 0.424 g of 5% Pd on activated carbon and 0.624 g (11.55 mmol) of sodium methoxide. The mixture was stirred under a hydrogen balloon overnight. The catalyst was then removed with the use of a fritted glass funnel and the filtrate concentrated in vacuo. The crude product was chromatographed through 100 g of silica gel using 10% MeOH in ether as the eluant to afford 1.17 g (78%) of the hydrogenated product. The spectral data for mixture of diastereomers obtained were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.33−7.12 (m, 5H), 4.21−4.05 (m, 1H), 3.74−3.34 (m, 5H), 2.66 (dd, 1H, J = 13.5, 6 Hz), 2.57−2.40 (m, 2H), 2.15−1.84 (m, 5H), 1.77−1.71 (m, 0.5H), 1.55−0.95 (m, 1.5 H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.8, 171.7, 139.2, 138.1, 129.2, 129.0, 128.8, 128.6, 126.5, 68.2, 67.7, 61.2, 61.1, 61.0, 59.4, 42.3, 42.0, 37.9, 37.8, 35.3, 34.7, 32.2, 31.0, 29.5, 29.1, 27.2, 26.1; IR (neat/NaCl) 3384 br, 3026, 2933, 2878, 1653, 1617, 1559, 1497, 1457, 1411, 1364, 1325, 1185, 1050, 752, 703 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 300 (M + 41, 3), 289 (M + 30, 3), 288 (M + 29, 12), 262 (M + 3, 3), 261 (M + 2, 28), 260 (M + 1, 100), 258 (4), 253 (3), 242 (4), 229 (2), 228 (6), 119 (3); HRMS (EI) *m/e* calcd for $C_{15}H_{18}ON$ 228.1388; found 228.1388 (M − CH_3O).

(9*S*)-1-Aza-4-benzyl-9-[(*tert*-butyldimethylsiloxy)-methyl]-2-oxobicyclo[4.3.0]nonane. To a solution of the hydrogenated compound (3.823 g, 14.8 mmol) in 30 mL of CH_2Cl_2 were added TBDMSCl (4.449 g, 29.5 mmol) and DBU (4.73 g, 31.0 mmol). The mixture was stirred at rt for 1 h and then transferred to a separatory funnel. The organic layer was separated and then washed with a 10% citric acid solution followed by saturated aqueous $NaHCO_3$ solution. The CH_2Cl_2 was removed under reduced pressure and the crude product chromatographed through ca. 250 g of silica gel using 60% ether/hexane as eluant to afford 4.945 g of the protected amide (90%). The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.32−7.14 (m, 5H), 4.20−4.12 (m, 0.5H), 4.05−4.00 (m, 0.5H), 3.94 (dd, 0.5H, J = 9.9, 4.2 Hz), 3.83 (dd, 0.5H, J = 9.9, 5.1 Hz),

3.75–3.64 (m, 2H), 3.46–3.41 (m, 1H), 2.68 (dd, 1H, J = 13.2, 6.0 Hz), 2.57–2.40 (m, 2H), 2.10–1.63 (m, 8H), 0.86 and 0.88 (two s, 9H), 0.04, 0.02, 0.01 and 0 (four s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 168.9, 168.3, 139.2, 129.0, 128.3, 126.2, 63.0, 62.0, 60.0, 59.6, 58.1, 57.8, 42.7, 42.3, 38.4, 35.8, 33.0, 31.1, 26.6, 25.8, 24.7, 18.1, −5.4, −5.5; IR (neat/NaCl) 2951, 2928, 2855, 1735, 1700, 1653, 1637, 1565, 1522, 1465, 1437, 1252,;1095, 836, 777, 700, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 403 (M + 30, 8), 402 (M + 29, 18), 376 (M + 3, 12), 375 (M + 2, 42), 374 (M + 1, 100), 372 (10), 359 (19), 358 (47), 317 (20), 316 (54), 242 (16), 91 (15); HRMS (EI) *m/e* calcd for $C_{22}H_{35}O_2NSi$ 373.2437; found 373.2433.

(9*S*)-1-Aza-4-benzyl-9-[(*tert*-butyldimethylsiloxy)-methyl]-3-hydroxy-2-oxobicyclo[4.3.0]non-3-ene (28a,b). An oven-dried two-neck flask was charged with 8 mL of THF and 0.66 g (6.5 mmol) of diisopropylamine. To this mixture was added 2.53 mL (4.06 mmol) of a 1.6 M *n*-butyllithium in hexanes solution at −78 °C. The mixture was stirred at −78 °C for 0.5 h, and then the protected amide (0.739 g, 1.98 mmol) in 10 mL of THF was cannulated slowly into the flask. The flask originally containing the protected amide was washed with an additional 2 mL of THF and these washings added to the reaction. The resulting mixture was stirred at −78 °C for another 45 min. Following this period, oxygen was bubbled through the reaction for 30 min at −78 °C. The reaction was quenched by the addition of a saturated aqueous $NaHSO_3$ solution to the flask. The reaction was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed through 75 g of silica gel using 30% ether/hexane as the eluant to afford 0.487 g (63%) of compound **28a,b** as a white solid. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.32–7.19 (m, 5H), 6.42 and 6.40 (two s, 1H), 4.16–4.04 (m, 2H), 3.83–3.45 (m, 4H), 2.21–1.67 (m, 5H), 1.67–1.41 (m, 1H), 0.87 (s, 9H), 0.04 and 0.02 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 162.2, 161.2, 139.0, 138.8, 138.5, 128.4, 126.2, 117.0, 115.0, 62.8, 62.2, 58.6, 58.0, 57.8, 57.3, 35.7, 35.5, 32.1, 32.0, 31.9, 31.1, 29.7, 26.7, 26.0, 25.9, 25.8, 18.2, 18.1, 1.0, −5.4, −5.5; IR (neat/NaCl) 3328, 2955, 2930, 2883, 2857, 1636, 1463, 1327, 1319, 1288, 1254, 1216, 1107, 1007, 837, 776, 702, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 416 (M + 29), 390 (M + 3, 12), 389 (M + 2, 42), 388 (M + 1, 100), 373 (11), 372 (30), 331 (16), 330 (46), 91 (14), 75 (10), 73 (8), 57 (19); HRMS (EI) *m/e* calcd for $C_{22}H_{33}O_3NSi$ 387.2230; found 387.2269. Anal. Calcd for $C_{22}H_{33}O_3NSi$: C, 68.18; H, 8.59; N, 3.62. Found: C, 67.93; H, 8.52; N, 3.62.

(6*S* and 6*R*,9*S*)-1-Aza-3-amino-4-benzyl-9-[(*tert*-butyldimethylsiloxy)methyl]-2-oxobicyclo[4.3.0]non-3-ene (29a,b). Ammonia gas was passed through a solution of compound **28a,b** (2.751 g, 7.11 mmol) in 36 mL of MeOH at 0 °C until the solution was saturated. The reaction mixture was stirred at rt under a rubber septum for three days. The MeOH was removed under reduced pressure, and the crude product was chromatographed through 150 g of silica gel using a gradient elution from 30% ether/hexane to 80% ether/hexane as eluant in order to afford 0.638 g (23%) of compound **29a**, 1.235 g (45%) of compound **29b**, and 0.842 g (31%) of recovered starting material. The spectral data for **29a** were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.30–7.16 (m, 5H), 4.19–4.11 (m, 1H), 4.01 (dd, 1H, J = 9.6, 4.8 Hz), 3.81–3.70 (m, 4H), 3.44 (A of AB, 1H, J = 15.6 Hz), 3.37 (B of AB, 1H, J = 15.6 Hz), 2.15–1.86 (m, 5H), 1.52–1.39 (m, 1H), 0.856 (s, 9H), 0.02 and 0.01 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 161.4, 138.3, 131.7, 128.4, 128.3, 126.2, 126.0, 113.4, 62.4, 58.4, 56.7, 37.1, 33.6, 31.9, 25.7, 18.0, −5.5, −5.6; IR (neat/NaCl) 3448, 3357, 3061, 3026, 2955, 2929, 2882, 2857, 1635, 1583, 1453, 1322, 1254, 1116, 1006, 837,776, 735, 701, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 416 (M + 30, 8), 415 (M + 29, 17), 389 (M + 3, 13), 388 (M + 2, 43), 387 (M + 1, 100), 386 (M, 16), 385 (7), 372 (14), 371 (32), 330 (12), 329(31), 163 (6); HRMS (EI) *m/e* calcd for $C_{22}H_{34}O_2N_2Si$ 386.2390; found 386.2390.

The spectral data for **29b** were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.29–7.15 (m, 5H), 4.07 (br s, 1H), 3.78–3.53 (m, 5H), 3.49 (A of AB, 1H, J = 15.3 Hz), 3.42 (B of AB, 1H, J = 15.3 Hz), 2.13 (d, 2H, J = 9 Hz), 2.03–1.98 (m, 1H), 1.93–1.66 (m, 3H), 0.859 (s, 9H), 0.03 and 0.002 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 162.5, 138.4, 131.8, 128.6, 128.4, 126.3, 115.7, 65.8, 62.8, 57.9, 57.6, 37.5, 33.7, 31.1, 26.5, 25.9, 18.2, 15.2, −5.4, −5.5; IR (neat/NaCl) 3451, 3354, 3060, 3026, 2954, 2929, 2882, 2857, 1664, 1635, 1583, 1494, 1451, 1331, 1257, 1116, 1096, 1054, 1007, 838, 777, 733, 701, 667 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 415 (M + 29, 17), 389 (M + 3, 11), 388 (M + 2, 39), 387 (M + 1, 100), 386 (15), 372, (13), 371 (33), 330 (13), 329 (37), 91 (22), 57 (30), 55 (17); HRMS (EI) *m/e* calcd for $C_{22}H_{34}O_2N_2Si$ 386.2390; found 386.2411.

(6*S* and 6*R*,9*S*)-1-Aza-4-benzyl-9-[(*tert*-butyldimethylsiloxy)methyl]-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-2-oxobicyclo[4.3.0]non-3-ene. To a solution of compound **29a** (0.638 g, 1.65 mmol) in 10 mL of CH_2Cl_2 was added HOBt (0.313 g, 2.31 mmol) and *N*-(carbobenzyloxy)-L-alanine (0.443 g, 1.98 mmol). The mixture was stirred at 0 °C for 5 min and then EDCI (0.411 g, 2.15 mmol) added. The resulting mixture was allowed to warm to rt and stirred overnight. When complete, the solution was transferred to a separatory funnel, the layers were separated, and the organic phase was washed with saturated $NaHCO_3$, 10% citric acid, and saturated NaCl solution. The CH_2Cl_2 was removed under reduced pressure, and the crude product was chromatographed through 50 g of silica gel using 1% MeOH in ether to afford 0.346 g (35%) of the tripeptide (isomer a) as a white solid. The spectral data for isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.22 (s, 1H), 7.31–7.15 (m, 10H), 5.95–5.92 (d, 1H, J = 7.2 Hz), 5.17 (A of AB, 1H, J = 12 Hz), 5.04 (B of AB, 1H, J = 12 Hz), 4.51–4.39 (m, 1H), 4.11 (br s, 1H), 3.92 (dd, 1H, J = 5.1, 5.1 Hz), 3.86–3.77 (m, 1H), 3.71 (app d, 1H, J = 9.9 Hz), 3.50 (s, 2H), 2.25 (dd, 1H, J = 17.1, 5.1 Hz), 2.16–1.86 (m, 5H), 1.46 (d, 3H, J = 6.9 Hz), 0.86 (s, 9H), 0.02 and 0 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.2, 161.1, 155.7, 140.4, 137.5, 136.2, 129.1, 128.4, 128.3, 128.0, 127.8, 126.4, 123.2, 66.6, 62.3, 58.6, 56.0, 51.0, 39.1, 34.0, 31.6,25.9, 25.7, 18.8, 18.0, −5.5, −5.6; IR (neat/NaCl) 3278 br, 3061, 3030, 2955, 2930, 2884, 2857, 1718, 1659, 1623, 1522, 1496, 1453, 1361, 1321, 1253, 1116, 1072, 1029, 1005, 837, 778, 739, 701, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 599 (M + 8, 25), 593 (M + 2, 38), 592 (M + 1, 100), 534 (20); HRMS (FAB) *m/e* calcd for $C_{33}H_{46}O_5N_3Si$ (M + 1) 592.3207; found 592.3206.

The tripeptide (isomer b) was made in an identical fashion with a yield of 67%. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.21 (s, 1H), 7.34–7.17 (m, 10H), 5.85 (d, 1H, J = 7.2 Hz), 5.15 (A of AB, 1H, J = 12.3 Hz), 5.09 (B of AB, 1H, J = 12.3 Hz), 4.50 (t, 1H, J = 6.9 Hz), 4.09 (br s, 1H), 3.91–3.66 (m, 3H), 3.60 (A of AB, 1H, J = 16.5 Hz), 3.53 (B of AB, 1H, J = 16.5 Hz), 2.30 (dd, 1H, J = 16.8, 3.9 Hz), 2.10–1.68 (m, 5H), 1.49 (d, 3H, J = 6.9 Hz), 0.87 (s, 9H), 0.04 and 0 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.0, 161.9, 142.2, 137.5, 129.2, 128.5, 128.4, 128.0, 126.5, 123.4, 66.9, 62.7, 57.9, 56.7, 50.9, 39.6, 34.2, 31.0, 29.7, 26.9, 25.9, 18.9, 18.2, −5.5, −5.6; IR (neat/NaCl) 3272 br, 3063, 3031, 2954, 2931, 2883, 2857, 1718, 1685, 1653, 1624, 1522, 1497, 1447, 1363, 1348, 1251, 1115, 1094, 1051, 911, 838, 777, 734, 701 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 594 (M + 3, 15), 593 (M + 2, 47), 592 (M + 1, 100), 591 (M, 21), 590 (13), 534 (18), 387 (27), 386 (12), 385 (16); HRMS (FAB) *m/e* calcd for $C_{33}H_{46}O_5N_3Si$ (M + 1) 592.3207; found 592.3197.

(6*S* and 6*R*,9*S*)-1-Aza-4-benzyl-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]-non-3-ene. The tripeptide (isomer a) (76.7 mg, 0.130 mmol) was dissolved in a solution comprised of 0.5 mL of 2 N H_2SO_4 and 1.5 mL of THF. The mixture was stirred at rt overnight. The solution was transferred into a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude product was then chromatographed through silica gel with the use of 8% MeOH in ether as eluant to afford 40.8 mg (64%) of the deprotected product (isomer a) as a white solid and 13.0 mg (21%) of the recovered starting material. The spectral data for isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.25 (s, 1H), 7.32–7.14 (m, 10H), 5.97–5.90 (m, 2H), 5.14 (A of AB, 1H, J = 12 Hz), 5.05 (B of AB, 1H, J = 12 Hz), 4.48 (app t, 1H, J = 7.2 Hz), 4.06 (app q, 1H, J = 7.0 Hz), 3.81–3.78 (m, 1H), 3.74–3.67 (m, 1H), 3.59–3.44 (m, 3H), 2.30 (dd, 1H, J =

17.1, 4.8 Hz), 2.08–1.98 (m, 3H), 1.45 (d, 3H, J = 7.2 Hz), 1.41–1.36 (m, 2H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.3, 162.8, 155.9, 141.3, 137.2, 136.2, 129.2, 128.5, 128.4, 128.0, 126.6, 123.2, 66.9, 66.0, 65.8, 62.5, 56.3, 50.9, 39.2, 34.2, 31.8, 27.1, 18.8; IR (neat/NaCl) 3280 br, 3062, 3030, 2972, 2933, 2879, 1718, 1700, 1685, 1654, 1617, 1540, 1522, 1497, 1452, 1320, 1246, 1069, 738, 701, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity): 478 (M + 1, 21), 460 (14), 434 (7), 386 (100), 371 (53); HRMS (FAB) *m/e* calcd for $C_{27}H_{32}O_5N_3$ 478.2342; found 478.2293 (M + 1).

The deprotected compound (isomer b) was made in an identical fashion to afford a 91% yield of the desired product along with a 7% yield of the recovered starting material. The spectral data for the isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.66 (s, 1H), 7.31–7.17 (m, 10H), 5.73 (d, 1H, J = 7.5 Hz), 5.07 (s, 2H), 4.64 (t, 1H, J = 7.2 Hz), 4.18 (br s, 1H), 3.83–3.67 (m, 2H), 3.53 (s, 3H), 3.49–3.13 (m, 1H), 2.33 (dd, 1H, J = 17.1, 3.6 Hz), 2.10–1.90 (m, 4H), 1.62–1.53 (m, 1H), 1.44 (d, 3H, J = 5.7 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.5, 163.5, 155.9, 143.3, 137.3, 136.1, 129.3, 128.5, 128.4, 128.0, 126.6, 123.5, 67.0, 65.5, 59.4, 57.4, 50.6, 39.4, 34.2, 30.8, 26.9, 19.2; IR (neat/NaCl) 3271 br, 3060, 3032, 2978, 2941, 2881, 1700, 1628, 1506, 1448, 1366, 1325, 1254, 1070, 1048, 956, 913, 736, 702 cm^{-1}; LRMS (FAB) *m/e* (rel intensity): 478 (M + 1, 61), 389 (11), 369 (28), 344 (6), 277 (100); HRMS (FAB) *m/e* calcd for $C_{27}H_{32}O_5N_3$ (M + 1), 478.2342; found 478.2344.

(6*S* and 6*R*,9*S*)-1-Aza-4-benzyl-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-carboxy-2-oxobicyclo[4.3.0]non-3-ene (30a,b). To a solution of the deprotected alcohol (isomer a, 0.228 g, 0.48 mmol) in 5 mL of acetone was added Jones reagent (about 0.5 mL, 0.62 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then rt for 1.5 h. Once complete, the reaction was diluted with MeOH and then the salt in the solution removed by filtration through a plug of glass wool. The filtrate was concentrated *in vacuo* to afford a crude oil, which was dissolved in water. Ammonium chloride was added in order to saturate the solution, and then the mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered through a glass fritted funnel, and concentrated *in vacuo*. The crude acid was further purified by HPLC using 50% MeOH/H_2O as eluant to afford compound **30a** as a white solid (0.158 g, 67%). The spectral data for isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 9.64 (br s, 1H), 8.61 and 8.50 (two s, 1H), 7.30–7.21 (m, 10H), 6.98 (br s, 0.4H), 5.99 (d, 0.6H, J = 6.3 Hz), 5.17, 5.13 and 5.07 (three s, 1.6H), 4.80 and 4.76 (two s, 0.4H), 4.42 (app q, 1.6H, J = 7.5 Hz), 4.25 (app t, 0.4H, J = 6.6 Hz), 3.93 (br s, 1H), 3.55 (A of AB, 0.8H, J = 12 Hz), 3.47 (B of AB, 0.8H, J = 12 Hz), 3.13 and 3.26 (two s, 0.4H), 2.35 and 2.30 (two s, 2H), 2.20, 2.14 and 2.10 (three s, 2H), 1.92 (br s, 1H), 1.52 (app t, 1H, J = 9 Hz), 1.41 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 174.3, 172.5, 162.1, 155.7, 144.7, 137.4, 136.4, 129.3, 128.6, 128.5, 128.3, 127.8, 126.5, 123.0, 66.5, 58.3, 55.9, 50.9, 39.1, 33.1, 32.5, 28.2, 18.8; IR (neat/NaCl) 3281 br, 3060, 3031, 2977, 2939, 1717, 1653, 1625, 1522, 1497, 1456, 1326, 1245, 1214, 1069, 737, 701 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 551 (M + 60, 20), 535 (M + 44, 18), 523 (M + 32, 19), 514 (M + 23, 27), 493 (M + 2, 33), 492 (M + 1, 100), 446 (13), 386 (20), 377 (29), 370 (24), 349 (33), 347 (26); HRMS (FAB) *m/e* calcd for $C_{27}H_{30}O_6N_3$ (M + 1) 492.2135; found 492.2135.

Compound **30b** was made in an identical fashion with a yield of 72%. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 10.12 (br s, 1H), 8.39 (s, 1H), 7.29–7.14 (m, 10H), 5.81 (d, 1H, J = 6.9 Hz), 5.07 (A of AB, 1H, J = 12 Hz), 5.02 (B of AB, 1H, J = 12 Hz), 4.49 (d, 1H, J = 8.1 Hz), 4.40 (t, 1H, J = 6.6 Hz), 3.84–3.71 (m, 1H), 3.65 (A of AB, 1H, J = 15.6 Hz), 3.43 (B of AB, 1H, J = 15.6), 2.31 and 2.26 (two s, 2H), 2.23–2.17 (m, 1H), 2.09–1.98 (m, 2H), 1.74–1.59 (m, 1H), 1.39 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 173.5, 172.3, 162.5, 155.9, 145.7, 137.1, 136.2, 129.3, 128.6, 128.4, 128.0, 127.9, 126.7, 123.7, 66.8, 58.1, 56.3, 50.6, 38.8, 33.4, 31.4, 28.1, 18.8; IR (neat/NaCl) 3296 br, 3025, 2982, 2927, 2812, 1713, 1645, 1515, 1501, 1448, 1351, 1301, 1240, 1078, 1053, 750, 712 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 514 (M + 23, 19) 493 (M + 2, 34), 492 (M + 1, 100), 446 (20), 377 (55), 356 (11); HRMS (FAB) *m/e* calcd for $C_{27}H_{30}O_6N_3$ (M + 1) 492.2135; found 492.2139.

(6*S* and 6*R*,9*S*)-1-Aza-4-benzyl-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-methoxy-L-(phenylalaninocarbonyl)-2-oxobicyclo[4.3.0]non-3-ene Methyl Ester (31a,b). To a solution of compound **30a** (70.0 mg, 0.143 mmol) in 3 mL of CH_2Cl_2 were added 27.0 mg (0.20 mmol) of HOBt, 36.9 mg (0.17 mmol) of L-phenylalanine methyl ester, and 37.0 mg (0.37 mmol) of 4-methylmorpholine. The mixture was stirred at 0 °C for 5 min and then 35.4 mg (0.18 mmol) of EDCI added. The resulting mixture was allowed to warm to rt and stirred overnight. The solution was transferred into a separatory funnel, the layers were separated, and the organic layer was washed with saturated $NaHCO_3$, 10% citric acid, and saturated NaCl solutions. The CH_2Cl_2 was then removed under reduced pressure and the crude product chromatographed through 20 g of silica gel using 3% methanol in ether as eluant to afford compound **31a** (83.2 mg, 90%). The spectral data for **31a** were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.09 (s, 1H), 7.36–7.10 (m, 15H), 5.73 (d, 1H, J = 7.2 Hz), 5.11 (A of AB, 1H, J = 12 Hz), 5.02 (B of AB, 1H, J = 12 Hz), 4.84 (q, 1H, J = 7.1 Hz), 4.55–4.43 (m, 2H), 3.83–3.73 (m, 1H), 3.68 (s, 3H), 3.57–3.43 (m, 2H), 3.14 (A of ABX, 1H, J_{AB} = 13.8 Hz, J_{AX} = 5.7 Hz), 2.96 (B of ABX, 1H, J_{AB} = 13.8 Hz, J_{BX} = 7.5 Hz), 2.23–1.94 (m, 5H), 1.51–1.43 (m, 1H), 1.42 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.8, 171.3, 170.5, 161.8, 155.8, 141.4, 137.3, 136.1, 129.2, 129.1, 128.6, 128.5, 128.4, 128.1, 128.0, 126.9, 126.7, 123.2, 66.9, 59.6, 55.4, 53.2, 52.2, 50.9, 39.3, 37.8, 34.1, 31.0, 26.8, 19.2; IR (neat/NaCl) 3283 br, 3060, 3031, 2949, 1734, 1718, 1700, 1685, 1664, 1636, 1540, 1522, 1506, 1497, 1456, 1244, 1215, 1070, 1049, 740, 701, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 653 (M + 1, 27), 448 (11), 386 (56), 307 (100); HRMS (FAB) *m/e* calcd for $C_{37}H_{41}O_7N_4$ 653.2975; found 653.2977.

Compound **31b** was made in an identical fashion with a yield of 87%. The spectral data for the isomer b were as follows: ^{1}H NMR ($CDCl_3$/300 MHz) δ 8.34 (s, 1H), 7.57 (d, 1H, J = 8.1 Hz), 7.32–7.02 (m, 15H), 5.65 (d, 1H, J = 7.5 Hz), 5.13 (A of AB, 1H, J = 12.3 Hz), 5.08 (B of AB, 1H, J = 12.3 Hz), 4.77 (app q, 1H, J = 6.9 Hz), 4.65 (t, 1H, J = 7.2 Hz), 4.53 (d, 1H, J = 8.7 Hz), 3.64 (s, 3H), 3.56 (A of AB, 1H, J = 16.5 Hz), 3.38 (B of AB, 1H, J = 16.5 Hz), 3.09–2.94 (m, 2H), 2.33–2.23 (m, 2H), 2.08–1.82 (m, 4H), 1.63–1.50 (m, 1H), 1.43 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.8, 171.1, 170.4, 162.7, 155.9, 143.5, 137.2, 136.1, 136.0, 129.4, 129.1, 128.8, 128.6, 128.5, 128.3, 128.1, 126.8, 126.6, 123.3, 67.0, 58.6, 57.1, 53.5, 52.2, 50.7, 39.5, 38.2, 38.1, 33.8, 31.3, 29.7, 27.5, 19.2; IR (neat/NaCl) 3085 br, 3062, 3029, 2951, 1735, 1685, 1653, 1624, 1522, 1506, 1497, 1456, 1363, 1339, 1251, 1215, 1072, 1029, 740, 701, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 653 (M + 1, 100), 645 (17), 605 (9); HRMS (FAB) *m/e* calcd for $C_{37}H_{41}O_7N_4$ 653.2975; found 653.2962.

3,3-Dimethyl-4-pentenoic Acid. The synthesis was identical to that described for 3-phenyl-4-pentenoic acid. Yield = 76%. ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.92 (dd, 1H, J = 17.1, 10.8 Hz), 5.04–4.95 (m, 2H), 2.34 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 178.1, 146.4, 111.1, 46.5, 36.0, 26.9; IR (neat/NaCl) 3087–2931 br, 2687 br, 1707, 1641, 1472, 1457, 1411, 1367, 1309, 1256, 1185, 1140, 998, 916, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 130 (M + 2, 8), 129 (M + 1, 63), 112 (9), 111 (68), 87 (17), 84 (3), 83 (100); HRMS (EI) *m/e* calcd for $C_7H_{12}O_2$ 128.0837; found 128.0840.

(2*S*)-1-(3,3-Dimethyl-4-pentenoyl)-2-(hydroxymethyl)-pyrrolidine. The synthesis was identical to that described for compound **19**. Yield = 83%. The spectra data for the pair of amide rotomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.96 (dd, 1H, J = 17.4, 10.8 Hz), 5.02–4.93 (m, 2H), 4.44 (br s, 1H), 4.28–4.20 (m, 1H), 3.65–3.41 (m, 4H), 2.37 (A of AB, 1H, J = 13.2 Hz), 2.29 (B of AB, 1H, J = 13.2 Hz), 2.08–1.76 (m, 3H), 1.66–1.56 (m, 1H), 1.18 (s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 172.5, 146.8, 110.6, 67.0, 60.5, 48.8, 46.1, 36.7, 28.0, 27.1, 26.9, 24.3; IR (neat/NaCl) 3396 br, 3082, 2962, 2876, 1617, 1457, 1424, 1364, 1355, 1323, 1253, 1188, 1054, 1007, 912, 676 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 240 (M + 29, 17), 213 (M + 2, 32), 212 (M + 1, 100), 211 (M, 8), 210 (7), 194 (7), 128 (8), 103 (7), 102 (43), 100 (6), 84 (8), 70 (10); HRMS (EI) *m/e* calcd for $C_{12}H_{21}O_2N$ 211.1572; found 211.1549.

(2S)-2-[(Benzyloxy)methyl]-1-(3,3-dimethyl-4-pentenoyl)pyrrolidine (32). Compound **32** was made in an identical fashion to compound **17** in a 78% yield. ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.36−7.28 (m, 5H), 5.97 (dd, 1H, J = 17.7, 11.1 Hz), 4.99−4.89 (m, 2H), 4.36−4.31 (m, 0.7H), 4.08−4.02 (m, 0.3H), 3.64 (dd, 1H, J = 9.9, 3.3 Hz), 3.54−3.37 (m, 3H), 2.33−2.19 (m, 2H), 2.06−1.82 (m, 4H), 1.16 and 1.14 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 170.1, 147.5, 128.5, 128.3, 127.8, 127.5, 127.4, 110.3, 73.3, 73.1, 71.1, 70.2, 57.3, 56.3, 48.2, 46.2, 45.6, 45.3, 36.7, 28.7, 27.5, 27.2, 27.1, 26.9, 24.3, 21.8; IR (neat/NaCl) 3084, 3064, 3030, 2962, 2873, 1722, 1638, 1496, 1453, 1413, 1364, 1314, 1272, 1196, 1103, 1028, 1003, 917, 737, 698 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 330 (M + 28, 11), 304 (M + 3, 4), 303 (M + 2, 32), 302 (M + 1, 100), 224 (5), 210 (4), 195 (7), 194(22), 192(8), 180 (4), 119 (14), 91 (11); HRMS (EI) *m/e* calcd for $C_{19}H_{28}O_2N$ 301.2120; found 301.2128.

(2S)-2-[(Benzyloxy)methyl]-5-methoxy-1-(3,3-dimethyl-4-pentenoyl)pyrrolidine (37). An oven-dried three-neck flask was charged with compound **32** (3.013 g, 10.0 mmol), 20 mL of MeOH, and tetraethylammonium tosylate (0.181 g, 0.60 mmol). The flask was then equipped with a carbon rod anode and platinum wire cathode. The mixture was degassed under a slow stream of nitrogen for 5 min. The solution was then electrolyzed at a constant current of 51.4 mA until 2.5 F/mol had been passed. The MeOH was removed under reduced pressure and the crude oil chromatographed through 250 g of silica gel using a gradient elution from 40% ether/hexane to 80% ether/hexane in order to afford 2.172 g (66%) of the methoxylated amide **37** along with 0.628 g (21%) of the recovered starting material **32**. The spectral data for the pair of amide rotomers were as follows: ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.32 (s, 5H), 5.99−5.88 (m, 1H), 5.62 (d, 0.5H, J = 5.1 Hz), 5.04 (d, 0.5H, J = 5.1 Hz), 5.00−4.88 (m, 2H), 4.57−4.46 (m, 2H), 4.32−4.24 (m, 0.5H), 4.17−4.08 (m, 0.5H), 3.91 (dd, 0.5H, J = 9.0, 3.9 Hz), 3.53 (t, 0.5H, J = 8.4 Hz), 3.44−3.34 (m, 2H), 3.28 and 3.23 (two s, 3H), 2.56−2.31 (m, 2H), 2.12−1.98 (m, 2H), 1.87−1.74 (m, 2H), 1.17, 1.16, 1.13 and 1.12 (four s, 6H); ^{13}C NMR ($CDCl_3$/75Hz) δ 171.8, 170.8, 147.1, 138.4, 137.7, 128.2, 128.0, 127.5, 127.4, 127.3, 127.1, 110.4, 110.2, 89.6, 89.5, 87.2, 74.5, 73.1, 72.9, 71.7, 56.8, 56.1, 55.5, 53.7, 45.3, 44.7, 36.4, 36.3, 30.7, 30.3, 27.4, 27.2, 26.8, 26.7, 25.8; IR (neat/NaCl) 2959, 2931, 2876, 1724, 1700, 1653, 1456, 1399, 1363, 1273, 1197, 1071, 1028, 912, 698, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity): 332 (M + 1, 4), 300 (13), 191 (21), 190 (100), 100 (6), 91 (9); HRMS (EI) *m/e* calcd for $C_{20}H_{30}O_3N$ (M + 1) 332.2226; found 332.2226.

(9S)-1-Aza-4-(1-chloro-1-methylethyl)-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]nonane (35a,b). Compounds **35a** and **35b** were made in a fashion identical to that described for the synthesis of the compounds represented by structure **22**. Yield = 89%. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.38−4.15 (m, 2H), 3.77−3.65 (m, 2H), 3.59−3.46 (m, 2H), 2.73−2.31 (m, 3H), 2.20−1.97 (m, 3H), 1.78−1.71 (m, 0.5H), 1.64 and 1.57 (two s, 6H), 1.54−1.23 (m, 1.5H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.0, 170.7, 71.9, 71.6, 67.8, 67.4, 61.3, 61.1, 60.5, 59.0, 45.6, 45.0, 33.8, 33.6, 32.4, 31.3, 31.1, 30.7, 30.6, 29.6, 29.5, 27.4, 26.2; IR (neat/NaCl) 3350 br, 2974, 2927, 2876, 1673, 1653, 1636, 1617, 1456, 1374, 1353, 1324, 1083, 1057, 733, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 250 (M + 5, 4), 238 (12), 212 (6), 211 (24), 210 (100), 209 (6), 208 (7), 192 (9), 184 (4), 178 (6), 100 (8), 61 (5); HRMS (EI) *m/e* calcd for $C_{12}H_{20}O_2N^{35}Cl$ 245.1183; found 245.1179; calcd for $C_{12}H_{20}O_2N^{37}Cl$ 247.1153; found 247.1186.

(9S)-1-Aza-9-(hydroxymethyl)-4-isopropyl-2-oxobicyclo[4.3.0]nonane. The synthesis was identical to that described for (9*S*)-1-aza-4-benzyl-9-(hydroxymethyl)-2-oxobicyclo[4.3.0]-nonane above. Yield = 92%. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.14 (br s, 1H), 4.25−4.12 (m, 1H), 3.89−3.40 (m, 3H), 2.51 (td, 1H, J_t=18 Hz, J_d=6 Hz), 2.18−1.92 (m, 4H), 1.76−1.36 (m, 4H), 1.15−0.98 (m, 1H), 0.92 (d, 6H, J = 6.3 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.7, 171.4, 67.2, 67.0, 60.9, 60.8, 60.7, 60.5, 59.4, 39.4, 38.8, 35.3, 35.1, 32.6, 32.4, 32.3, 32.0, 31.6, 31.0, 27.0, 26.0, 19.2, 19.1, 19.0; IR (neat/NaCl) 3370 br, 2959, 2873, 1617, 1458, 1413, 1367, 1326, 1051 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 252 (M + 41, 10), 241 (M + 30, 9), 240 (M + 29, 32), 214 (M + 3, 7), 213 (M + 2, 60), 212 (M + 1, 100), 211 (M, 14), 210 (15), 194 (15), 181 (5), 180 (16), 100(6); HRMS (EI) *m/e* calcd for $C_{12}H_{21}O_2N$ 211.1572; found 211.1580.

(9S)-1-Aza-9-[(*tert*-butyldimethylsiloxy)methyl]-4-isopropyl-2-oxobicyclo[4.3.0]nonane. The synthesis was done in a fashion identical to that reported above for (9*S*)-1-azo-4-benzyl-9-[(*tert*-butyldimethylsiloxy)methyl]-2-oxobicyclo[4.3.0]-nonane. Yield = 79%. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.20−4.13 (m, 0.5H), 4.07−4.01 (m, 0.5H), 3.97 (dd, 0.5H, J = 9.6, 4.2 Hz), 3.85 (dd, 0.5H, J = 9.9, 4.5 Hz), 3.75 (dd, 0.5H, J = 9.9, 2.7 Hz), 3.68 (dd, 0.5H, J = 9.6, 2.1 Hz), 3.50−3.34 (m, 1H), 2.44 (td, 1H, J_t = 17.4, J_d = 6 Hz), 2.10−1.04 (m, 9H), 0.91, 0.89 and 0.88 (three s, 15H), 0.04, 0.03, 0.02, and 0.01 (four s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 169.5, 169.0, 62.8, 62.0, 60.1, 58.8, 58.1, 57.8, 40.2, 39.5, 35.7, 33.2, 32.5, 32.0, 31.2, 26.6, 25.9, 25.7, 24.8, 18.5, 18.3, 18.1, −5.4, −5.5; IR (neat/NaCl) 2957, 2930, 2858, 1646, 1472, 1446, 1413, 1388, 1362, 1325, 1253, 1101, 837, 777, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 355 (M + 30, 8), 354 (M + 29, 22), 328 (M + 3, 10), 327 (M + 2, 36), 326 (M + 1, 100), 325 (M, 8), 324 (12), 311 (18), 310 (51), 269 (15), 268 (47), 194 (18); HRMS (EI) *m/e* calcd for $C_{18}H_{35}O_2NSi$ 325.2437; found 325.2455.

(9S)-1-Aza-9-[(*tert*-butyldimethylsiloxy)methyl]-3-hydroxy-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene. The synthesis was identical to that reported for compounds **28a** and **28b** above. Yield = 66%. The spectral data for the mixture of diastereoisomers were as follows: ^{1}H NMR ($CDCl_3$/300 MHz) δ 6.22 and 6.23 (two s, 1H), 4.15−4.03 (m, 2H), 3.74−3.67 (m, 2H), 3.65−3.56 (m, 1H), 2.32 (dd, 1H, J = 16.2, 4.8 Hz), 2.24−1.77 (m, 4H), 1.63−1.50 (m, 1H), 1.06 (d, 3H, J = 7.2 Hz), 0.97 (d, 1.5H, J = 6.6 Hz), 0.96 (d, 1.5H, J = 6.9 Hz), 0.89 and 0.86 (two s, 9H), 0.04, 0.03, 0.02, and 0 (four s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 162.4, 161.5, 136.6, 123.7, 121.6, 62.8, 62.3, 58.5, 58.1, 57.7, 57.4, 32.2, 31.2, 27.7, 27.5, 26.9, 26.8, 26.6, 26.1, 25.9, 25.8, 25.7, 20.9, 20.8, 19.0, 18.1, −5.5, −5.6; IR (neat/NaCl) 3352 br, 2960, 2930, 2895, 2856, 1631, 1617, 1465, 1374, 1306, 1206, 1156, 1083, 1007, 837, 775 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 368 (M + 29, 15), 341 (M + 2, 23), 340 (M + 1, 100), 338 (7), 324 (43), 282 (46), 208 (8), 115 (24), 75 (13), 61 (11), 57 (20), 56 (11); HRMS (EI) *m/e* calcd for $C_{18}H_{33}O_3NSi$ 339.2230; found 339.2188.

(6S,9S)-1-Aza-3-amino-9-[(*tert*-butyldimethylsiloxy)-methyl]-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (38a) and (6*R*,9*S*)-1-aza-3-amino-9-[(*tert*-butyldimethylsiloxy)-methyl]-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (38b). Compounds **38a** and **38b** (isomer a, 28%; isomer b, 30%; mixture of isomer a and b, 3%) were made in an identical fashion to compounds **29a** and **29b**. A 13% yield of recovered starting material was obtained from this experiment. The spectral data for the isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.22−4.15 (m, 1H), 3.99 (dd, 1H, J = 9.9, 4.8 Hz), 3.79 (dd, 1H, J = 9.9, 2.4 Hz), 3.76−3.66 (m, 2H), 3.61 (br s, 1H), 2.75−2.66 (m, 1H), 2.29 (dd, 1H, J = 15.9, 5.1 Hz), 2.24−2.16 (m, 1H), 2.14−1.94 (m, 3H), 1.64−1.51 (m, 1H), 1.08 (d, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 6.3 Hz), 0.89 (s, 9H), 0.06 and 0.04 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 161.8, 129.0, 121.0, 62.5, 58.4, 56.8, 32.0, 28.1, 28.0, 25.9, 25.7, 20.4, 18.8, 18.0, −5.6; IR (neat/NaCl) 3357, 3422, 2958, 2929, 2857, 1664, 1635, 1584, 1457, 1362, 1322, 1254, 1117, 1098, 1005, 837, 776, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 368 (M + 30, 6), 367 (M + 29, 16), 355 (M + 17, 5), 341 (M + 3, 9), 340 (M + 2, 39), 339 (M + 1, 100), 338 (M, 11), 337 (9), 324 (18), 323 (50), 282 (13), 281 (43); HRMS (EI) *m/e* calcd for $C_{18}H_{34}O_2N_2Si$ 338.2389; found 338.2393. The spectral data for the isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.10−4.04 (m, 1H), 3.79 (dd, 1H, J = 9.6, 3.0 Hz), 3.66−3.47 (m, 4H), 2.75−2.66 (m, 1H), 2.28 (dd, 1H, J = 16.5, 4.2 Hz), 2.07−1.71 (m, 5H), 1.06 (d, 3H, J = 7.2 Hz), 0.97 (d, 3H, J = 6.6 Hz), 0.88 (s, 9H), 0.05 and 0.02 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 162.6, 129.0, 122.8, 62.6, 57.6, 57.4, 31.0, 28.0, 27.8, 26.3, 25.7, 20.4, 18.7, 18.0, −5.6, −5.7; IR (neat/NaCl) 3423, 3354, 2957, 2930, 2858, 1664, 1630, 1583, 1472, 1444, 1362, 1344, 1330, 1258, 1117, 855, 837, 777, 668 cm^{-1}; GCMS (PCI) *m/e* (rel intensity) 367 (M + 29, 9), 356 (M + 18, 6), 355 (M + 17, 17), 341 (M + 3, 6), 340 (M + 2, 36), 339 (M + 1, 100), 338 (M, 7), 337 (6), 324

(14), 323 (48), 282 (12), 281 (46); HRMS (FAB) *m/e* calcd for $C_{18}H_{35}O_2N_2Si$ (M + 1) 339.2467; found 339.2447.

(6*S*,9*S*)-1-Aza-9-[(*tert*-butyldimethylsiloxy)methyl]-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer a) and (6*R*,9*S*)-1-Aza-9-[(*tert*-butyldimethylsiloxy)methyl]-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer b). The syntheses were done in a fashion identical to that described above. The yield for isomer a was 71%. The spectral data for the isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.81 (s, 1H), 7.36–7.29 (m, 5H), 6.19 (d, 1H, J = 8.1 Hz), 5.16, 5.12, 5.10 and 5.06 (four s, 2H), 4.43 (app t, 1H, J = 7.2 Hz), 4.12 (br s, 1H), 3.87–3.74 (m, 2H), 3.30 (br s, 1H), 2.78–2.67 (m, 1H), 2.47 (dd, 1H, J = 16.5, 4.5), 2.30–2.20 (m, 1H), 2.13–1.90 (m, 3H), 1.64–1.51 (m, 1H), 1.45 (d, 3H, J = 6.3 Hz), 1.12 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6 Hz), 0.86 (s, 9H), 0.02 and −0.01 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.4, 161.5, 155.9, 148.7, 136.3, 128.3, 127.9, 127.8, 127.7, 121.0, 66.7, 65.7, 62.5, 58.7, 58.0, 56.1, 50.9, 31.7, 30.0, 29.2, 26.2, 25.7, 19.9, 19.1, 18.8, 18.2, 18.0, 15.1, −5.5, −5.6; IR (neat/NaCl) 3329 br, 2956, 2928, 2856, 1718, 1653, 1617, 1540, 1522, 1506, 1457, 1395, 1364, 1339, 1253, 1214, 1117, 1069, 837, 779, 697, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 593 (M + 50, 48), 584 (M + 41, 12), 576 (M + 33, 33), 544 (M + 1, 100), 535 (9), 524 (12); HRMS (FAB) *m/e* calcd for $C_{29}H_{46}O_5N_3Si$ 544.3207; found 544.3153 (M + 1). The yield for isomer b was 84%. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.94 (s, 1H), 7.34–7.26 (m, 5H), 5.96 (d, 1H, J = 7.2 Hz), 5.10 (s, 2H), 4.45 (app t, 1H, J = 7.2 Hz), 4.06 (br s, 1H), 3.71–3.59 (m, 3H), 2.84–2.75 (m, 1H), 2.49 (dd, 1H, J = 16.8, 3.6 Hz), 2.13, 2.01 and 1.98 (three s, 3H), 1.92–1.74 (m, 2H), 1.43 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.3 Hz), 0.92 (d, 3H, J = 6.9 Hz), 0.87 (s, 9H), 0.02 and 0 (two s, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.6, 162.0, 155.6, 150.4, 136.3, 128.2, 127.8, 121.4, 66.5, 62.5, 57.8, 56.6, 50.6, 31.1, 30.0, 28.8, 26.7, 25.7, 20.1, 19.1, 18.8, 18.0, −5.6, −5.7; IR (neat/NaCl) 3307 br, 2954, 2929, 2856, 1718, 1653, 1617, 1559, 1540, 1517, 1457, 1339, 1251, 1219, 1116, 1071, 1029, 854, 837, 777, 696, 673 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 595 (M + 52, 25), 585 (M + 42, 21), 576 (M + 33, 53), 544 (M + 1, 100), 530 (20), 519(11); HRMS (FAB) *m/e* calcd for $C_{29}H_{46}O_5N_3Si$ (M + 1) 544.3207; found 544.3207.

(6*S*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-(hydroxymethyl)-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer a) and (6*R*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-(hydroxymethyl)-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer b). The syntheses were done in an identical fashion to that described above for the benzyl substituted building blocks. The yield for isomer a was 59% with 10% recovered starting material. The spectral data for the isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.35 (s, 6H), 5.14 (A of AB, 1H, J = 12 Hz), 5.08 (B of AB, 1H, J = 12 Hz), 4.42 (d, 1H, 6.6 Hz), 4.09 (q, 1H, J = 7.8 Hz), 3.89–3.77 (m, 1H), 3.73 and 3.69 (two s, 1H), 3.57–3.50 (m, 1H), 2.75 (app t, 8.4 Hz), 2.54 (dd, 1H, J = 10.8, 4.8 Hz), 1.64–1.51 (m, 2H), 1.46 (d, 3H, J = 7.5 Hz), 1.13 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.6, 163.1, 149.6, 136.2, 128.5, 128.1, 120.9, 67.0, 66.0, 62.6, 56.5, 50.8, 32.1, 30.2, 29.9, 29.3, 27.2, 20.0, 19.2, 18.9, 18.7; IR (neat/NaCl) 3286 br, 3034, 2965, 2935, 2974, 1718, 1700, 1685, 1653, 1617, 1522, 1506, 1448, 1364, 1339, 1248, 1069, 737, 698 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 431 (M + 2, 19), 430 (M + 1, 74), 307 (30), 289 (17), 279 (15), 225 (23), 155 (26), 154 (100), 138 (21), 137 (41), 136 (45); HRMS (FAB) *m/e* calcd for $C_{23}H_{32}O_5N_3$ (M + 1) 430.2342; found 430.2340. The yield for isomer b was 69% with 26% recovered starting material. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.34 (s, 6H), 5.10 (s, 2H), 4.56 (app d, J = 6.9 Hz), 4.12 (br s, 1H), 3.79–3.62 (m, 2H), 3.51 (dd, 1H, J = 5.4, 5.1 Hz), 2.78 (app t, 1H, J = 6.6 Hz), 2.52 (dd, 1H, J = 16.5, 3.0 Hz), 2.15, 2.10 and 2.05 (three s, 2H), 1.92 (br s, 2H), 1.76–1.62 (m, 1H), 1.41 (d, 3H, J = 6.9 Hz), 1.10 (d, 3H, 6.3 Hz), 0.93 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.8, 163.5, 155.7, 151.4, 136.1, 128.3, 127.9, 121.4, 66.7, 65.3, 59.2, 57.3, 50.3, 31.0, 30.0, 29.1, 26.9, 20.2, 19.2, 19.1; IR (neat/NaCl) 3286 br, 3063, 3034, 2967, 2940, 2876, 1700, 1685, 1653, 1622, 1522, 1506, 1447, 1363, 1339, 1252, 1070, 1050, 736, 697 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 430 (M + 1, 30), 225 (36), 224 (22), 133 (19), 119 (34), 117 (100), 115 (23); HRMS (FAB) *m/e* calcd for $C_{23}H_{32}O_5N_3$ 430.2342; found 430.2327 (M + 1).

(6*S*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-carboxy-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer a) and (6*R*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-9-carboxy-4-isopropyl-2-oxobicyclo[4.3.0]non-3-ene (isomer b). The syntheses were done in a fashion identical to the benzyl substituted building blocks described above. The yield for isomer a was 53%. The spectral data for isomer a (two rotomers) were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 9.90 (br s, 1H), 8.36 (s, 1H), 7.34–7.30 (m, 5H), 6.99 (s, 0.4H), 5.99 (d, 0.6H, J = 6.6 Hz), 5.27–4.98 (m, 2H), 4.47–4.22 (m, 2H), 3.93 (br s, 1H), 2.84–2.69 (m, 1H), 2.56–2.39 (m, 2H), 2.28–2.15 (m, 2H), 1.95 (br s, 1H), 1.66 (br s, 1H), 1.39 (d, 3H, J = 6.3 Hz), 1.06 (d, 2H, J = 6.3 Hz), 0.95 (d, 2H, J = 6.0 Hz), 0.84 (br s, 2H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 174.3, 172.5, 162.4, 155.7, 152.1, 136.5, 128.4, 127.9, 127.7, 121.1, 120.9, 67.2, 66.6, 58.8, 58.4, 56.1, 52.5, 50.8, 32.8, 32.5, 30.1, 29.6, 28.6, 28.3, 20.4, 20.3, 19.0, 18.6, 17.9; IR (neat/NaCl) 3284 br, 3033, 2970, 2936, 2876, 1718, 1700, 1685, 1653, 1623, 1522, 1506, 1457, 1339, 1253, 1217, 1072, 1029, 775, 736, 669, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 466 (M + 33), 445 (M + 2, 27), 444 (M + 1, 100), 443 (M, 12), 398 (8), 349 (10); HRMS (FAB) *m/e* calcd for $C_{23}H_{30}O_6N_3$ (M + 1) 444.2134; found 444.2146. The yield for isomer b was 58%. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.63 (br s, 1H), 8.12 (s, 1H), 7.34 (s, 5H), 5.81 (d, 1H, J = 7.5 Hz), 5.11 (s, 2H), 4.50 (d, 1H, J = 9 Hz), 4.39 (t, 1H, J = 6.9 Hz), 3.87 (br s, 1H), 2.89 (app t, 1H, J = 6.6 Hz), 2.54 (dd, 1H, J = 16, 3.6 Hz), 2.33–2.08 (m, 4H), 1.87–1.76 (m, 1H), 1.39 (d, 3H, J = 6.6 Hz), 1.06 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 173.3, 172.3, 162.8, 155.9, 153.2, 136.3, 128.4, 128.0, 121.7, 66.8, 58.2, 56.4, 50.4, 31.6, 30.9, 29.8, 28.8, 28.0, 20.5, 19.1, 18.9; IR (neat/NaCl) 3287 br, 3033, 2968, 2874, 1718, 1700, 1685, 1653, 1636, 1623, 1559, 1540, 1522, 1507, 1457, 1339, 1252, 1216, 1071, 1029, 736, 698, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 466 (M + 23, 20), 445 (M + 2, 28), 444 (M + 1 100), 329 (29), 307 (18), 239 (33), 193 (17), 155 (17), 154 (73), 138 (19), 137 (35), 136 (53), 117 (33); HRMS (FAB) *m/e* calcd for $C_{23}H_{30}O_6N_3$ (M + 1) 444.2134; found 444.2122.

(6*S*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-4-isopropyl-9-(L-phenylalaninocarbonyl)-2-oxobicyclo-[4.3.0]non-3-ene Methyl Ester (36a) and (6*R*,9*S*)-1-Aza-3-[[*N*-(carbobenzyloxy)-L-alanyl]amino]-4-isopropyl-9-(L-phenylalaninocarbonyl)-2-oxobicyclo[4.3.0]non-3-ene Methyl Ester (36b). Compounds **36a** and **36b** (isomer a, 92%; isomer b, 84%) were made in an identical fashion to compounds **31a** and **31b**. The spectral data for isomer a were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.63 (s, 1H), 7.33–7.10 (m, 10H), 5.73 (d, 1H, 7.2 Hz), 5.13 (A of AB, 1H, J = 12 Hz), 5.06 (B of AB, 1H, J = 12 Hz), 4.83 (q, 1H, J = 6.9 Hz), 4.54 (dd, 1H, J = 7.8, 7.2 Hz), 4.43 (t, 1H, J = 7.2 Hz), 3.69 (s, 3H), 3.15 (A of ABX, 1H, J_{AB} = 13.8 Hz, J_{AX} = 5.4 Hz), 2.96 (B of ABX, 1H, J_{AB} = 13.8 Hz, J_{BX} = 7.2 Hz), 2.76 (app t, 1H, J = 6.6 Hz), 2.43 (dd, 1H, J = 17.4, 4.8 Hz), 2.27–1.98 (m, 4H), 1,66–1.56 (m, 1H), 1.45 (d, 3H, J = 7.2 Hz), 1.14 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.8, 171.4, 170.3, 162.0, 149.5, 136.2, 136.1, 129.2, 128.4, 128.3, 128.2, 128.0, 126.8, 120.9, 66.9, 59.6, 58.2, 55.3, 53.1, 52.2, 50.8, 37.8, 31.0, 30.2, 29.1, 26.4, 20.1, 19.0, 18.3; IR (neat/NaCl) 3300 br, 3062, 3033, 2966, 2875, 1734, 1718, 1685, 1653, 1540, 1526, 1456, 1362, 1339, 1244, 1214, 1069, 1029, 739, 700, 668 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 627 (M + 13, 14), 605 (M + 1, 100), 546 (25), 512 (17), 491 (40), 466 (13), 449 (17), 431 (23); HRMS (FAB) *m/e* calcd for $C_{33}H_{41}O_7N_4$ (M + 1) 605.2975; found 605.2954. The spectral data for isomer b were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.20 (s, 1H), 7.66 (d, 1H, J = 7.5 Hz), 7.37–7.08 (m, 10H), 5.73 (d, 1H, J = 7.8 Hz), 5.14 (s, 2H), 4.80 (q, 1H, J = 7.2 Hz), 4.71 (t, 1H, J = 7.5 Hz), 4.54 (d, 1H, J = 8.4 Hz), 3.62 (s, 3H), 3.01 (d, 2H, J = 6.9 Hz), 2.65 (t, 1H, J = 6.6 Hz), 2.48 (dd, 1H, J = 16.5, 3.9 Hz), 2.32 (dd, 1H, J = 12, 5.4 Hz), 2.16–2.04 (m, 2H), 1.99–1.69 (m, 3H), 1.40 (d, 3H, J = 7.2 Hz), 1.10 (d, 3H, 6.9 Hz), 0.75 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz/$CDCl_3$) δ 171.7, 171.5, 170.6,

162.6, 155.9, 151.0, 136.2, 136.1, 129.1, 128.4, 128.2, 128.1, 128.0, 126.8, 121.1, 66.9, 58.6, 57.0, 53.6, 52.0, 50.5, 38.3, 31.5, 30.4, 28.9, 27.9, 20.1, 19.6, 19.0, 18.3; IR (neat/NaCl) 3085 br, 3064, 3034, 2967, 2872, 1744, 1684, 1653, 1623, 1526, 1506, 1456, 1363, 1339, 1249, 1214, 1072, 1029, 740, 700 cm^{-1}; LRMS (FAB) *m/e* (rel intensity) 605 (M + 1, 100), 545 (7), 491 (9), 427 (10), 399 (32), 372 (11); HRMS (FAB) *m/e* calcd for $C_{33}H_{41}O_7N_4$ (M + 1) 605.2975; found 605.2950.

(6*R*,9*S*,12*S*)-1-Aza-3-(pyroglutamylamino)-4-benzyl-9-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxobicyclo[4.3.0]-nonene. A 100 mL single-neck round-bottom flask was charged with 920 mg (2.38 mmol) of (6*S*,9*R*)-1-aza-3-amino-4-benzyl-9-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxobicyclo-[4.3.0]nonene (**29b**), 369 mg (2.86 mmol) of L-pyroglutamic acid, 450 mg (3.33 mmol) of 1-hydroxybenzotriazole, and 30 mL of dichloromethane. This mixture was cooled to 0 °C and 638 mg (3.33 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride added. The reaction was warmed to room temperature and stirred for 5 days. At this time, the reaction was quenched with the addition of water. The layers were separated, and the organic layer was washed three times with a 5% solution of citric acid and three times with a saturated solution of sodium bicarbonate. The organic layer was then dried over magnesium sulfate, concentrated *in vacuo*, and chromatographed through 30 g of silica gel that was slurry packed with 5% methanol/dichloromethane. After elution with the same solvent mixture 518 mg (44% yield) of the desired product was obtained. The spectral data for the product was as follows: ^{1}H NMR (500 MHz/$CDCl_3$) δ 8.65 (br, 1H), 7.59 (br, 1H), 7.22 (m, 5H), 4.25 (m, 1H), 4.03 (m, 1H), 3.91 (dd, J = 10.1, 4.8 Hz, 1H), 3.82 (m, 1H), 3.67 (dd, J = 9.6, 1.9 Hz, 1H), 3.54 (A of AB, J = 15.4 Hz, 1H), 3.49 (B of AB, J = 15.4 Hz, 1H), 2.48 (m, 2H), 2.35−2.18 (m, 2H), 2.19−1.88 (m, 5H), 1.70 (m, 1H), 0.82 (s, 9H), 0.0 (d, 6H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 179.2, 177.7, 162.1, 143.9, 137.3, 129.2, 128.6, 126.6, 121.1, 62.7, 58.0, 57.8, 56.8, 39.3, 34.1, 31.2, 29.4, 27.0, 26.0, 25.9, 18.2; IR (neat/NaCl) 2920, 2845, 1660, 1690, 1480, 1383 cm^{-1}, LRMS (FAB) *m/e* (rel intensity) 498 (M + 1, 88), 185 (100), 387 (15), 255 (14); HRMS (FAB) *m/e* calcd for $C_{27}H_{39}N_3O_4Si$ 497.2710; found 497.2714.

(6*R*,9*S*,12*S*)-1-Aza-3-(pyroglutamylamino)-4-benzyl-9-carboxy-2-oxobicyclo[4.3.0]nonene. A 10 mL single-neck round-bottom flask was charged with 385 mg (0.77 mmol) of (6*S*,9*S*,12*S*)-1-aza-3-(pyroglutamylamino)-4-benzyl-9-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxobicyclo[4.3.0]nonene and 5 mL of acetone. The reaction was then cooled to 0 °C and 3 mL of Jones reagent added in a dropwise fashion. The mixture was stirred at 0 °C for 40 min, warmed to room temperature, and stirred for 2 h. Methanol was then added until a green color of Cr^{+3} salts persisted. The resulting mixture was filtered through glass wool, and the remaining salts were washed with methanol. The filtrate was concentrated *in vacuo*, and the resulting residue was triturated with ethyl acetate and dichloromethane. The mixture was filtered through Celite, and the solids were washed with ethyl acetate and dichloromethane. All the organic fractions were combined, dried over magnesium sulfate, and concentrated *in vacuo* to afford 121 mg of the impure carboxylic acid. This crude product mixture was carried on without further purification.

(6*R*,9*S*,12*S*)-1-Aza-3-(pyroglutamylamino)-4-benzyl-9-carbomethoxy-2-oxobicyclo[4.3.0]nonene. A 25 mL single-neck round-bottom flask was charged with 121 mg (0.30 mmol) of (6*S*,9*S*,12*S*)-1-aza-3-(pyroglutamylamino)-4-benzyl-9-carboxy-2-oxobicyclo[4.3.0]nonene, 4 mg (0.03 mmol) of 4-(dimethylamino)pyridine, 0.02 mL (0.50 mmol) of anhydrous methanol, and 3 mL of dichloromethane. This mixture was cooled to 0 °C and 63 mg (0.33 mmol) of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide added. The reaction was then warmed to room temperature, stirred for 18 h, and quenched with the addition of water. The resulting layers were separated, and then the organic layer was washed three times with a saturated solution of sodium bicarbonate, washed three times with a 5% solution of citric acid, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was chromatographed through 2 g of silica gel that was slurry packed using 25% methanol/ether and eluted with the same solvent mixture in order to afford 43 mg (14% over two steps) of the desired product as a white solid. The spectral data for the product were as follows: ^{1}H NMR (300 MHz/$CDCl_3$) δ 8.48 (br, 1H), 7.24 (m, 5H), 4.52 (d, J = 6 Hz, 1H), 4.25 (m, 1H), 3.81 (m, 1H), 3.72 (s, 3H), 3.47 (m, 2H), 2.30 (m, 9H), 1.69 (m, 1H); ^{13}C NMR (75 MHz/$CDCl_3$) δ 178.9, 172.4, 172.1, 161.5, 144.5, 137.1, 129.1, 128.7, 126.7, 124.0, 106.1, 57.5, 56.0, 52.4, 38.9, 33.8, 31.4, 29.4, 28.6, 26.0; LRMS (FAB) *m/e* (rel intensity) 412 (M + 1, 100), 369 (10), 301 (33); HRMS (FAB) *m/e* calcd for $C_{22}H_{26}N_3O_5$ 412.1872; found 412.1929.

(6*R*,9*S*,12*S*)-1-Aza-3-(pyroglutamylamino)-4-benzyl-9-carbamoyl-2-oxobicyclo[4.3.0]nonene (41b). A 25 mL single-neck round-bottom flask was charged with 42 mg (0.1 mmol) of (6*S*,9*S*,12*S*)-1-aza-3-(pyroglutamylamino)-4-benzyl-9-carbomethoxy-2-oxobicyclo[4.3.0]nonene, one crystal of sodium cyanide, and 5 mL of anhydrous methanol. Ammonia was then bubbled through the solution until it was saturated. The flask was sealed and then stirred at room temperature for 24 h. At this time, additional NH_3 was bubbled through and the solution stirred for three more days. Following completion of the reaction by TLC, the reaction mixture was concentrated *in vacuo* and then chromatographed by HPLC. A gradiant elution with 30% methanol/water to 50% methanol/water over 90 min was used with the product collected from 74 to 85 min in order to afford 27 mg (68%) of the desired conformationally restricted peptide analog as a white solid. The spectral data were as follows: ^{1}H NMR (300 MHz/CD_3OD) δ 7.26 (m, 5H), 4.88 (s, 4H), 4.38 (m, 2H), 3.75 (m, 1H) 3.72 (A of AB, J = 9 Hz, 1H), 3.43 (B of AB, J = 9 Hz, 1H), 2.28 (m, 9H), 1.71, m, 1H); ^{13}C NMR (75 MHz/CD_3OD) δ 181.7, 176.6, 175.5, 163.1, 149.6, 138.6, 130.3, 129.8, 127.9, 125.7, 60.1, 58.2, 57.9, 39.1, 34.1, 32.4, 30.6, 30.5, 26.9; LRMS (FAB) *m/e* (rel intensity) 419 (M + Na, 100), 397 (M + 1, 24), 176 (43); HRMS (FAB) *m/e* calcd for $C_{21}H_{24}N_4O_4Na$, 419.1695; found 419.1681.

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Supporting Information Available: Proton and carbon NMR data for all new compounds as well as HMQC and HMQC-TOCSY data for the hydrogenolysis product of **24a** and HMQC and NOESY data for compounds **38a** and **38b** (110 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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