Design and Synthesis of a Competent Pyrrolinone−Peptide Hybrid Ligand for the Class II Major Histocompatibility Complex Protein HLA-DR1

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Abstract: The design and synthesis of two pyrrolinone−peptide hybrid ligands (**3** and **20**) for the rheumatoid arthritis-associated class II MHC HLA-DR1 protein are described. The hybrids incorporate bispyrrolinones **4** and **21** as tetrapeptide mimics for amino acids VKQN (residues 309−312) of the virus hemagglutinin peptide HA 306−318 (PKY**VKQN**TLKLAT). Ligand construction employed our polypyrrolinone synthetic protocol, in conjunction with Fmoc-based solid-phase peptide synthesis. Bioaffinity studies reveal that hybrid ligand **3** bound the HLA-DR1 protein with affinity ($IC_{50} = 137$ nM) comparable to those of both the native HA 306−318 peptide ($IC_{50} = 89$ nM) and a control peptide ($IC_{50} = 176$ nM). This result demonstrates that the polypyrrolinone scaffold can be employed in the construction of bioactive peptide hybrid ligands, thus considerably expanding the scope and utility of the pyrrolinone scaffold.

The use of peptides as therapeutic agents is not usually feasible, given their poor pharmacokinetic properties.[1] Efforts to improve upon these unfavorable properties led to the development of pseudopeptides.[2] However, the design and development of medicinally useful peptidomimetics by this approach remains difficult because few generalizations can be made with regard to permissible dipeptide bond replacements. Recognizing that the pharmacokinetic shortcomings of peptides are not due exclusively to their susceptibility to proteolytic cleavage, Hirschmann, Smith, and Nicolaou in 1988 initiated an approach to peptidomimetic design wherein the peptide backbone is replaced by novel scaffolds but the critical side chains are retained. This approach led to the successful introduction of monosaccharide scaffolds as mimics of β-turns[3] and of the polypyrrolinone scaffold[4] as a mimic of β-strands/β-pleated sheets.

The design and synthesis of the 3,5,5-pyrrolin-4-one scaffold, a general β-strand non-peptide peptidomimetic, was first disclosed in 1992. These 3,5-linked polypyrrolinones, which are resistant to proteases, adopt extended conformations both in the

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solid state and in solution that closely resemble extended peptide β-strands. For example, trispyrrolinone **2**, based on the structure of the equine angiotensinogen fragment Leu-Leu-Val-Tyr-OMe (**1**, Figure 1), crystallized as a parallel β-pleated sheet, similar to **1**.[4a,d] Further analysis revealed a close correspondence between the amino acid side-chain trajectories and the carbonyl orientations of **2** and the known solid-state structure of the native peptide. Due to the observed formation of interstrand hydrogen bonds in the unit cell of **2**, we speculated that the pyrrolinone scaffold might be capable of binding to proteases and to other protein targets.[5] Related studies demonstrated that the poly-pyrrolinone scaffold adopts a similar extended conformation in solution.[6]
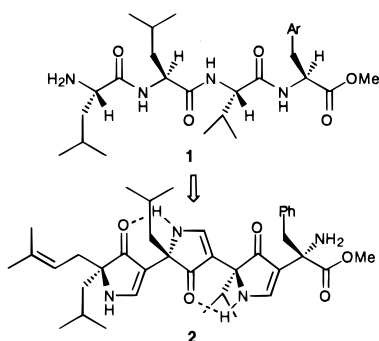
Figure 1. Tetrapeptide equine angiotensinogen fragment **1** and β-strand trispyrrolinone peptidomimetic **2**.

Subsequently we reported the design and synthesis of several potent mono- and bispyrrolinone inhibitors of the aspartic acid proteases renin[4e] and HIV-1 protease.[4c,f,h] Importantly, the HIV-1 protease inhibitors exhibited improved membrane transport properties, as characterized by the ratio of CIC_{95} to IC_{50},[7] relative to those of their peptidal counterparts. Favorable transport properties were suggested to be due to the presence of intramolecular hydrogen bonds between the NH and CO moieties of adjacent pyrrolinone rings (Figure 1). Thus, the pyrrolinone scaffold results in fewer molecules of solvation than found in amide bonds, thereby reducing the energy required for desolvation.[4c,8] The intramolecular hydrogen bonding also stabilizes the extended β-strand conformation of the pyrrolinone scaffold.

Taken together, these results suggested that the pyrrolinone scaffold holds considerable promise for the design of a wide variety of non-peptide β-strand mimics. Particularly intriguing was the possibility of employing this scaffold to construct pyrrolinone−peptide hybrids.[4i] Herein, we describe a full account of the design, synthesis, and evaluation of several pyrrolinone−peptide hybrid ligands for the class II major histocompatibility complex (MHC) protein HLA-DR1.

The class II MHC is a polymorphic[9] extracellular membrane-bound protein that is normally found on B lymphocytes, macrophages, and other specialized antigen-presenting cells.[10]

The primary role of this protein is to present antigenic peptides[11] derived from extracellular and intravesicular pathogens and toxins for inspection by the CD4 T cells of the immune system.[11b−d]

Inhibition of CD4 T cell self-antigen recognition comprises a promising approach for the treatment of numerous autoimmune diseases.[12] Recent elegant structural studies by Wiley and co-workers performed on the class II MHC protein led to the X-ray crystal structure (Figure 2) of the extracellular portion of this protein bound with the influenza virus hemagglutinin peptide fragment PKYVKQNTLKLAT (HA 306−318).[13] These studies demonstrate that the class II MHC protein exists as two noncovalently bound subunits (α and β). Each subunit is divided into two domains: the α_2 and β_2 domains anchor the protein to the cell membrane surface, while the α_1 and β_1 domains pair to form an antigen binding site.

Figure 2. Top angle view of the X-ray crystal structure[13] of HA 306−318 (purple) bound to the class II MHC HLA-DR1 protein binding site (blue).[15]

Normally, the class II MHC complex is stable only when a peptide is bound to the antigen presentation site.[14] For the MHC

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class II protein, these peptides usually consist of 10 or more amino acids that bind in an extended conformation.[13] Peptides that bind to the class II MHC protein have a wide variety of sequences; this feature is indicative of the ability of the MHC protein to present dissimilar antigenic peptides for inspection by immune system T cells. A common structural feature of high-affinity peptides for the class II MHC DR alleles is the presence of one or more anchor residues;[16] by convention, the anchor residue near the N-terminus is designated position 1. For the HA 306−318 peptide, the presence of a tyrosine anchor at position 1 and a leucine anchor at position 9 (Scheme 1), combined with hydrogen bond interactions between the HA 306−318 peptide backbone and the class II MHC HLA-DR1 protein accounts for a large portion of the total binding energy.[11,16c]

Design of a Pyrrolinone−Peptide MHC Class II Hybrid Ligand. Our design of a pyrrolinone−peptide hybrid ligand was based on the X-ray structure of the HA 306−318 peptide bound to the MHC protein HLA-DR1.[13] We examined the positions in the HA 306−318 peptide sequence using molecular modeling to identify sequences where the extended backbone geometry and hydrogen bonding network could be mimicked by the pyrrolinone scaffold. Additionally, a series of alanine scans of HA 306−318 (PKY**VKQN**TLKLAT) and related 7-mer ligands[17] suggested that the side chains of the **VKQN** sequence could be altered without significantly affecting binding. For example,

Scheme 1
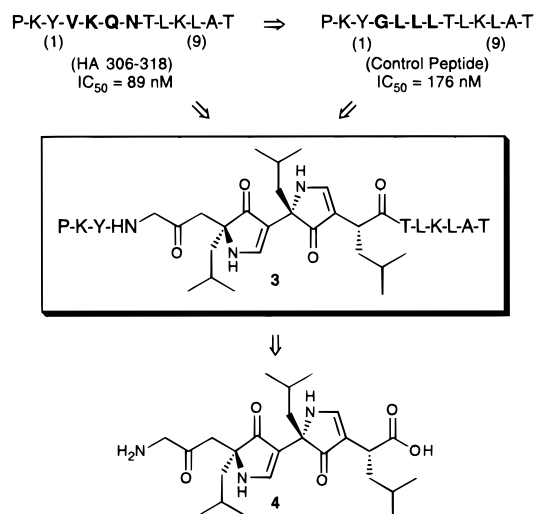
peptide PKY**GLLL**TLKLAT bound the HLA-DR1 protein with an IC$_{50}$ of 176 nM, comparable to an IC$_{50}$ of 89 nM for the native HA 306−318 peptide. We therefore reasoned that, if bispyrrolinone **4** (Scheme 1) serves as a viable replacement for the 2−5 amino acid **VKQN** sequence of HA 306−318, this
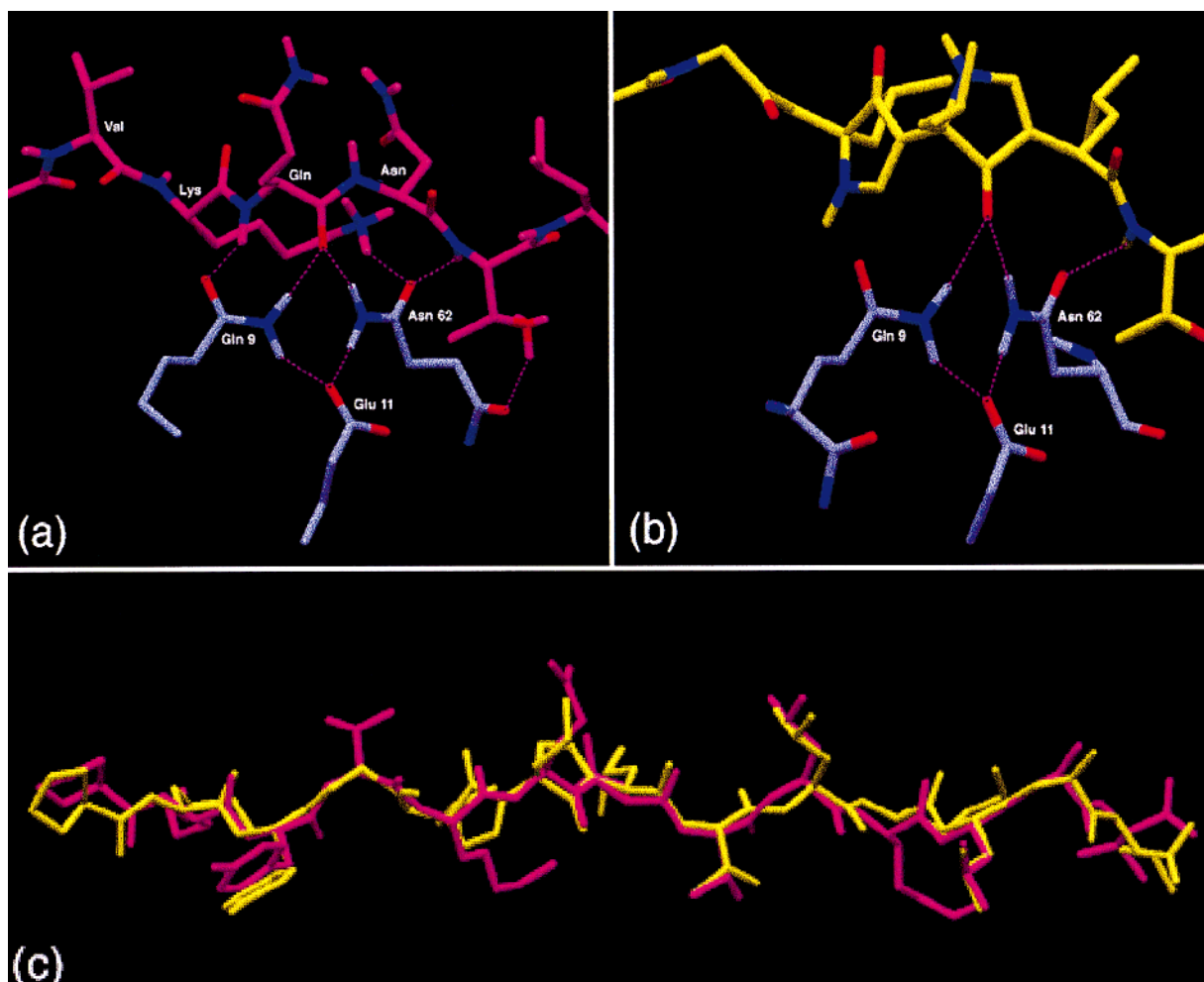
Figure 3. (a) X-ray crystal structure illustrating the position 2−5 backbone hydrogen bonds of HA 306−318 (purple) bound to the class II MHC HLA-DR1 protein (blue). (b) Molecular modeling prediction of the backbone hydrogen bonds of the position 2−5 bispyrrolinone mimic (yellow) bound to the MHC protein (blue). (c) Least-squares overlay of the backbone atoms of the X-ray structure of HA 306−318 (purple) and the predicted structure of the hybrid ligand **3** (yellow).

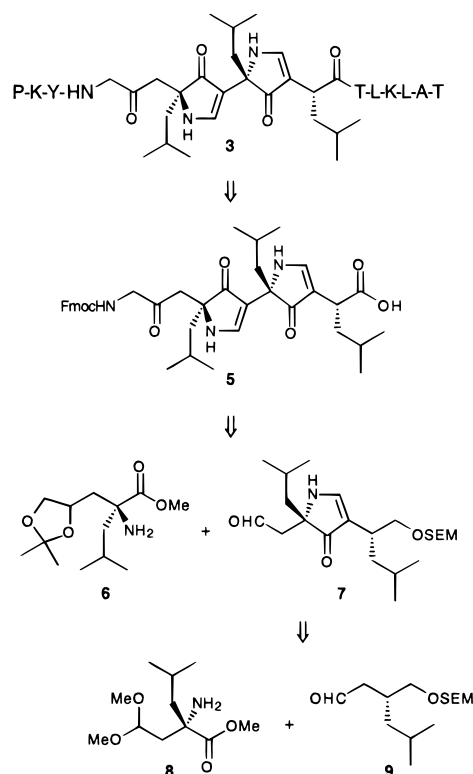would provide additional evidence that the pyrrolinone scaffold is truly a mimic of peptidal β-strands.

Molecular Modeling. The pyrrolinone−peptide hybrid was constructed by molecular modeling starting from a low-energy, extended conformation of the bispyrrolinone consistent with previously described solid-state and solution structures of related systems.[4j] Within the structure of the HLA-DR1 complex, the **VKQN** sequence of the HA 306−318 peptide was excised, and the bispyrrolinone **4** was inserted with the appropriate atoms superimposed to fit the backbone and side-chain residues of the **VKQN** sequence. The HA 306−318 peptide was replaced by the docked structure, and the system was subjected to a molecular dynamics minimization using MacroModel,[18] in which movements were permitted in the ligand but the binding site was kept fixed throughout the simulations as in the X-ray conformation of the MHC protein.[13]

The X-ray crystal structure of HA 306−318 bound to the HLA-DR1 protein[13] indicated that the peptide backbone at positions 3 and 4 is involved in a complex network of hydrogen bond interactions with Gln[9] and Asn[62] in the class II MHC binding site (Figure 3a). The results of the modeling studies indicated that displacement of the glutamine backbone nitrogen at position 4 to form the pyrrolinone ring results in the loss of a hydrogen bond to Gln[9] of the MHC DR1 protein (Figure 3b). Nonetheless, modeling revealed that the pyrrolinone carbonyl groups in **3** maintain their relative spacial orientations vis-à-vis the native HA 306−318 peptide, suggesting that the hydrogen bond network involving these carbonyls might remain intact. The molecular dynamics simulations also indicated that the modeled conformation of the bound hybrid ligand **3** (Figure 3c) would closely resemble the conformation of HA 306−318 bound to MHC derived from X-ray crystallography.[13] Other molecular dynamics simulations[19] using AMBER had suggested that hydrogen bonds at the position where the aminoketone group in **3** replaces a valine residue might not be stable due to increased flexibility associated with the lack of the Val isopropyl group. The same effect was noted in simulations of the **VKQN** → **GLLL** peptide analogue. Since there could be compensating factors such as the conformational preorganization afforded by the bispyrrolinone, the potential loss of a hydrogen bond interaction could not be accurately assessed. Consequently, the synthesis and testing of the hybrid was pursued.

Synthesis of Pyrrolinone−Peptide Hybrid Ligand 3. Analysis of **3** suggested that the peptide fragment TLKLAT (positions 6−11) could be constructed using solid-phase chemistry, followed by incorporation of bispyrrolinone **5** using Fmoc chemistry (Scheme 2). Removal of the Fmoc protecting group, addition of the remaining amino acids (PKY), and release of the hybrid from the resin with concomitant deprotection would
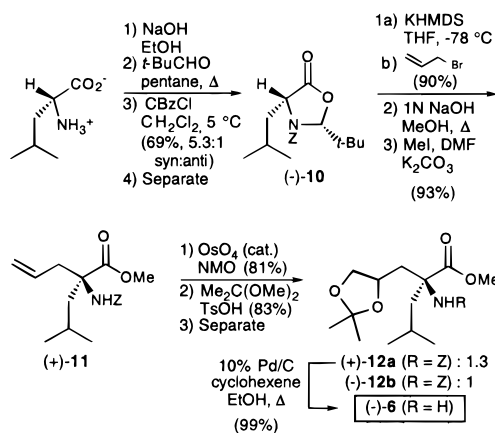
(15) This figure was generated using Molscript (Kraulis, P. J. *J. Appl. Crystallogr.* **1991**, *24*, 946) and Raster 3D (Bacon, D.; Anderson, W. F. *J. Mol. Graph.* **1988**, *6*, 219; Merritt, E. A.; Murphy, M. E. P. *Acta Crystallogr.* **1994**, *D50*, 869.).

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Scheme 2

then furnish the fully elaborated pyrrolinone−peptide ligand. Bispyrrolinone **5**, in turn, would be constructed via two iterations of our C-to-N pyrrolinone synthetic protocol,[4b,d] employing precursors **6**, **8**, and **9** (Scheme 2). Amino esters **6** and **8** would be readily available via the Seebach/Karady oxazolidinone method,[20] while aldehyde **9**[21] would derive from protection and ozonolysis of (*R*)-5-methyl-2-(2-methylpropyl)-4-hexen-1-ol.[4e]

The synthesis of bispyrrolinone **5** began with the preparation of amino ester **6** (Scheme 3). Condensation of the sodium salt of D-leucine with pivalaldehyde followed by treatment with benzyl chloroformate[4b] provided oxazolidinone (−)-**10** in 69% yield as a separable mixture (5.3:1) of syn and anti diastereomers; the desired syn diastereomer was isolated in 58% yield after chromatography. Alkylation with allyl bromide, followed by hydrolysis[20a] and treatment of the resulting acid with iodomethane, yielded (+)-**11**. Catalytic osmylation next provided a mixture (1.3:1) of diastereomeric diols, which were protected as their acetonides and separated to furnish (+)-**12a** and (−)-**12b**. Although both diastereomers could, in principle,

Scheme 3

be advanced, only the less polar diastereomer (+)-**12a** was employed. The relative stereochemistry of the acetonide stereogenic center was not established. Catalytic transfer hydrogenolysis[22] then furnished amino ester (−)-**6** in 99% yield.

Preparation of (−)-**7** entailed alkylation of (−)-**10** with prenyl bromide (Scheme 4), followed by hydrolysis and treatment of the resultant acid with iodomethane to furnish (+)-**13**. Ozonolysis, followed by protection of the resulting aldehyde as the dimethyl acetal and catalytic transfer hydrogenolysis[22] to remove the benzyl carbamate, provided (−)-**8** in 91% yield for three steps; condensation of this amine with aldehyde (+)-**9**,[21] followed by treatment with excess KHMDS, effected pyrrolinone ring formation in 78% yield. Hydrolysis of the acetal then gave aldehyde (−)-**7**.
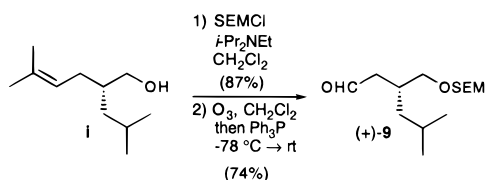
Scheme 4
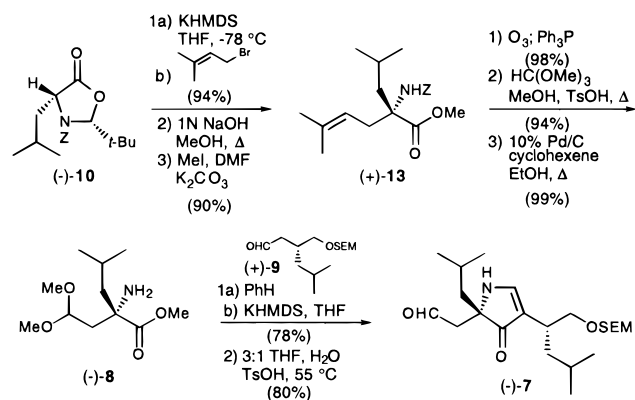
The preparation of pyrrolinone (−)-**7** via acetal (−)-**8** represents a departure from our standard iterative polypyrrolinone construction sequence, which entails a two-step oxidative cleavage (OsO$_4$ and NMO,[23] then NaIO$_4$) of an N-terminal prenyl group to generate the aldehyde. In cases when the carbon atom adjacent to the unsaturation in the pyrrolinone ring is not fully substituted, competing OsO$_4$ oxidation of the pyrrolinone ring has been observed.[4f] This oxidation does not occur when the adjacent carbon is fully substituted.

A second iteration of the pyrrolinone synthetic protocol employing amino ester (−)-**6** and aldehyde (−)-**7**, followed by Alloc protection of the pyrrolinone nitrogens, furnished (+)-**15** (Scheme 5). Removal of the acetonide and conversion of the primary alcohol in turn to the tosylate, bromide, and azide then furnished (+)-**17**. Reduction of the azide (Ph$_3$P),[24] followed by in situ protection of the resulting amine with FmocOSu,[25] gave (+)-**18**. Keto-acid (+)-**19** was then prepared by removal of the 2-(trimethylsilyl)ethoxymethyl (SEM) group, followed

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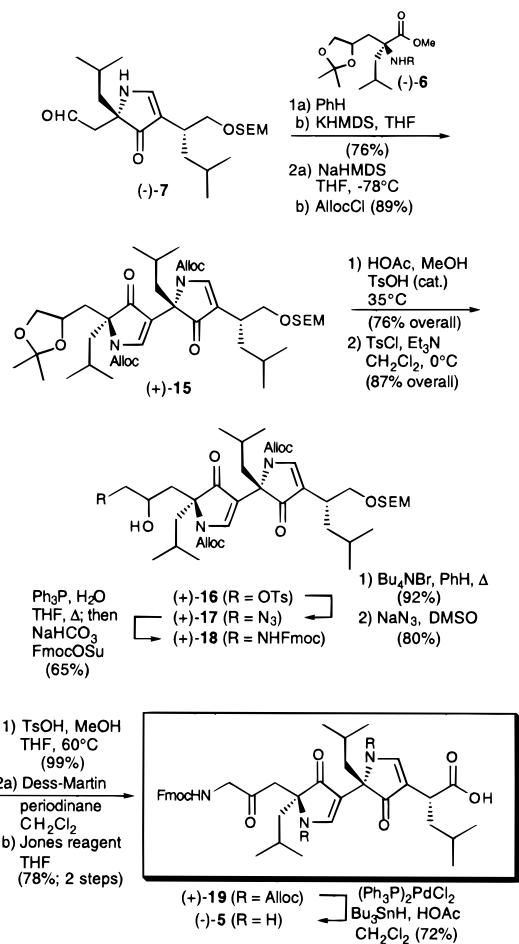(21) Aldehyde (+)-**9** was prepared from alcohol **i**[4e] as illustrated below:

(22) Jackson, A. E.; Johnstone, R. A. W. *Synthesis* **1976**, 685.
(23) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.
(24) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763.

Scheme 5

by a two-step oxidation employing the Dess–Martin periodinane[26] and Jones reagent. Removal of the Alloc protecting groups with catalytic (Ph$_3$P)$_2$PdCl$_2$ and excess Bu$_3$SnH[27] completed the synthesis of bispyrrolinone (−)-**5**.

With ample quantities of bispyrrolinone (−)-**5** available, we began construction of hybrid **3** by attaching amino acids 6−11 (TLKLAT) to Wang resin,[28] employing Fmoc-protected amino acids. Initially, union of bispyrrolinone (−)-**5** with HBTU[29] as the coupling agent proved problematic; the difficulty was overcome when moisture and oxygen were carefully excluded. Sequential addition of the remaining amino acids (PKY), followed by treatment with trifluoroacetic acid, released the pyrrolinone−peptide hybrid from the resin with simultaneous removal of the side-chain protecting groups. HPLC purification then yielded the MHC class II pyrrolinone−peptide ligand **3**.

Binding Affinity of the Pyrrolinone−Peptide Ligand 3 for the MHC Class II Protein HLA-DR1. Affinity binding competition experiments[30] revealed that hybrid **3** was, indeed, a competent ligand, having an IC$_{50}$ of 137 nM, compared with

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(26) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(27) (a) Guibé, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2365. (b) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
(28) Barany, G.; Merrifield, R. B. In *The Peptides: Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1980; Vol. 2, pp 1−284.
(29) (a) Dourtoglou, V.; Ziegler, J.-C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269. (b) Dourtoglou, V.; Gross, B.; Lambropoulou, V.; Zioudrou, C. *Synthesis* **1984**, 572.
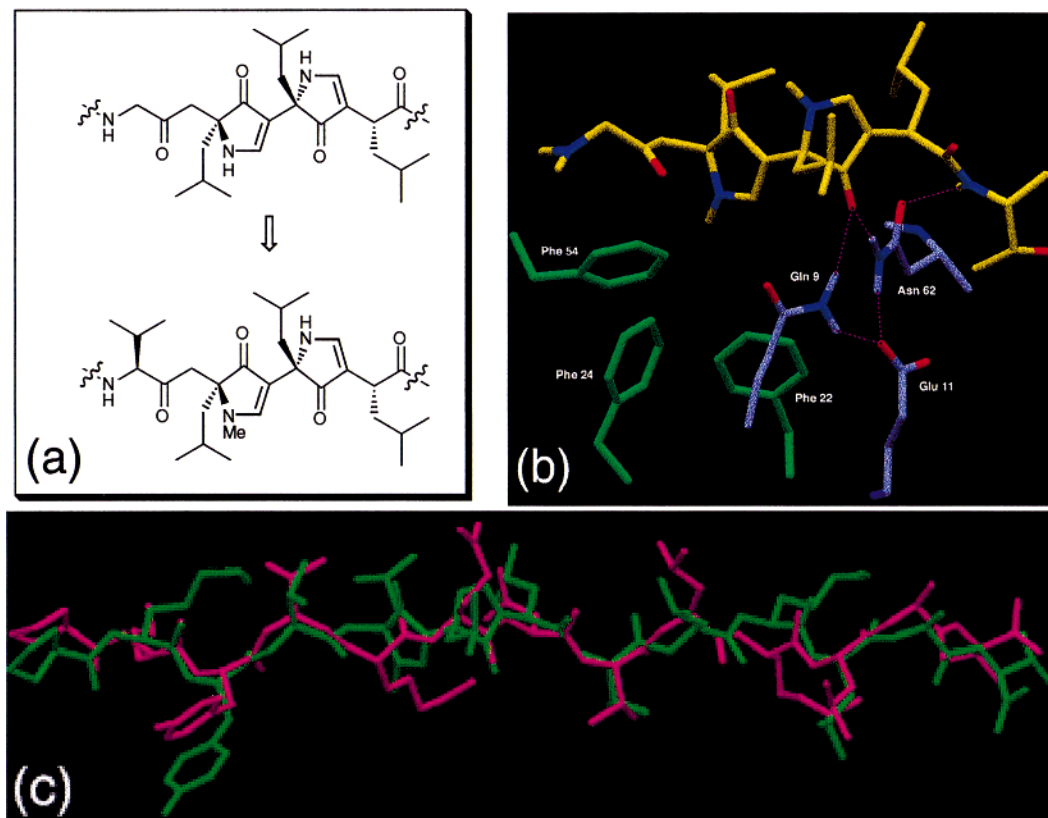
Figure 4. (a) Incorporation of an isopropyl side chain at position 2 and an N-methyl moiety at position 3 onto the bispyrrolinone scaffold. (b) Molecular modeling prediction of a potentially unfavorable hydrophobic interaction with the position 3 pyrrolinone NH. (c) Overlay of the prospective second generation pyrrolinone−peptide hybrid ligand (green) with the HA 306-318 peptide (purple).

89 nM for the HA 306−318 peptide (PKY**VKQN**TLKLAT) and 176 nM for the control peptide with the sequence PKY**GLLL**TLKLAT. The similarity of the affinity of **3** to that of the HA 306−318 peptide is intriguing, given the predicted loss (vide supra) of the hydrogen bond between Gln[9] of the MHC DR1 protein and the backbone NH at position 4 of HA 306−318, due to displacement of the NH to form the N-terminal pyrrolinone of the hybrid ligand. The observed binding was also of interest, given that the ketone at position 2, required only for synthetic purposes, was not expected to be as effective a hydrogen bond acceptor relative to the amide at position 2 of the HA 306−318 peptide (relative hydrogen bond acceptor index $\Sigma\beta_2^H \approx 0.50$ for a ketone vs $\Sigma\beta_2^H \approx 0.72$ for a secondary amide).[31] Notwithstanding these considerations, the similarity of the binding affinity of **3** to those of HA 306−318 and the control peptide suggests that incorporation of the bispyrrolinone did not significantly affect the overall conformation of the ligand, and that an energetically equivalent hydrogen bonding array was available. Alternately, the preorganization of the bispyrrolinone could have been a significant factor in counterbalancing losses in energy due to missing interactions. These issues will be addressed via X-ray crystallographic analysis of the hybrid ligand bound to the class II HLA-DR1 protein.

Design of a Second Generation Pyrrolinone−Peptide Hybrid Ligand. To increase the affinity of the pyrrolinone−peptide hybrid class II MHC ligand, we designed a second generation ligand (**20**) employing modified bispyrrolinone **21** (Scheme 6), incorporating both an isopropyl side chain at position 2 and an *N*-methyl pyrrolinone at position 3. The isopropyl side chain was introduced to mimic more closely the valine at position 2 of HA 306−318 (Figure 4a). We reasoned that this modification would induce further preorganization of the pyrrolinone−peptide hybrid by decreasing the conforma-

tional flexibility in this region. The second modification was introduced to prevent burying a pyrrolinone NH in a region that

Scheme 6
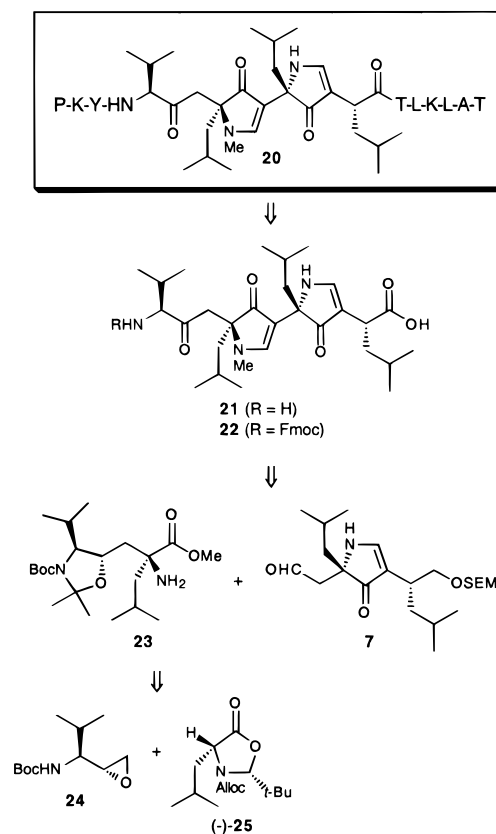
is predominantly hydrophobic [i.e., a pocket formed by a cluster of three phenylalanine residues (Figure 4b)]. From the synthetic perspective, *N*-methylation of the pyrrolinone ring appeared ideal in this regard. Importantly, the structure and conformation of the prospective second generation hybrid ligand (**20**) generated by molecular modeling[18] revealed good overall correspondence with the native HA 306−318 peptide (Figure 4c).

Synthesis of the Second Generation Hybrid Ligand 20. The requisite *N*-methyl bispyrrolinone **22** (Scheme 6) was again envisioned to derive via our pyrrolinone synthesis by coupling amino ester **23** with aldehyde **7**, the former available via reaction of epoxide **24** with the enolate of known oxazolidinone (−)-**25**.[4b,d] Incorporation of **22** into the pyrrolinone−peptide hybrid would then follow directly from the construction of hybrid **3**.

Our point of departure for the synthesis of amino ester **23** (Scheme 7) was aldehyde (−)-**26**, which was prepared from

Scheme 7
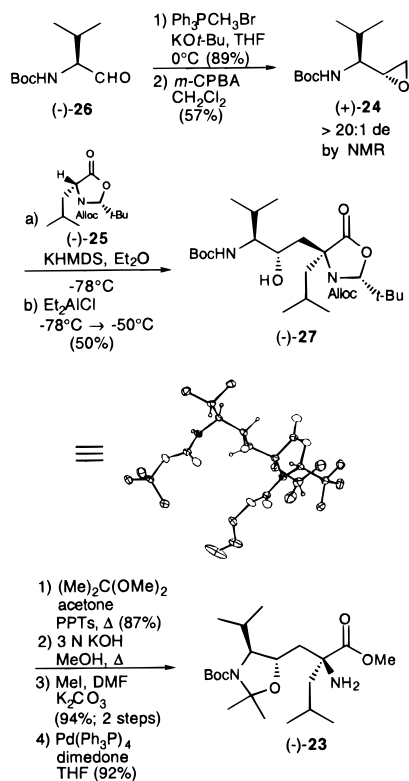
N-Boc L-valine in two steps.[32] Wittig olefination using Ph₃-PCH₃Br and KO*t*-Bu in THF at 0 °C provided the desired olefin with no detectable loss of optical purity.[33] Treatment with *m*-CPBA then provided epoxide (+)-**24** with greater than 20:1 de (NMR). The high stereoselectivity of this process is presumed to derive from the ability of the NHBoc moiety to direct the approach of the *m*-CPBA.[34] Employing methodology previously developed in our laboratory,[4f,35] treatment of the resulting epoxide with the potassium enolate of oxazolidinone (−)-**25**,

followed by addition of Et₂AlCl (7 equiv), yielded alcohol (−)-**27** in 50% yield. The structure and stereochemistry of (−)-**27** were confirmed by single-crystal X-ray analysis. Following epoxide opening, the hydroxyl and carbamate nitrogen were then protected as the acetonide. Hydrolysis of the oxazolidinone,[20a] treatment of the resulting acid with iodomethane, and removal of the Alloc carbamate[36] provided amino ester (−)-**23** in 86% yield for the three steps.

Coupling of amino ester (−)-**23** with aldehyde (−)-**7** via our now standard procedure was achieved in 68% yield (Scheme 8). Chemoselective installation of the N-terminal pyrrolinone methyl group[37] then entailed treatment with 1.0 equiv each of NaHMDS and methyl iodide; the yield was 55%. The reaction selectivity was confirmed by the disappearance of the non-hydrogen-bonded NH signals in both the IR and 500-MHz ¹H NMR spectra. Protection of the C-terminal pyrrolinone nitrogen as the allyl carbamate then gave (+)-**28**, which upon treatment with excess *p*-TsOH followed by FmocOSu provided (−)-**29** in 72% overall yield.

Scheme 8
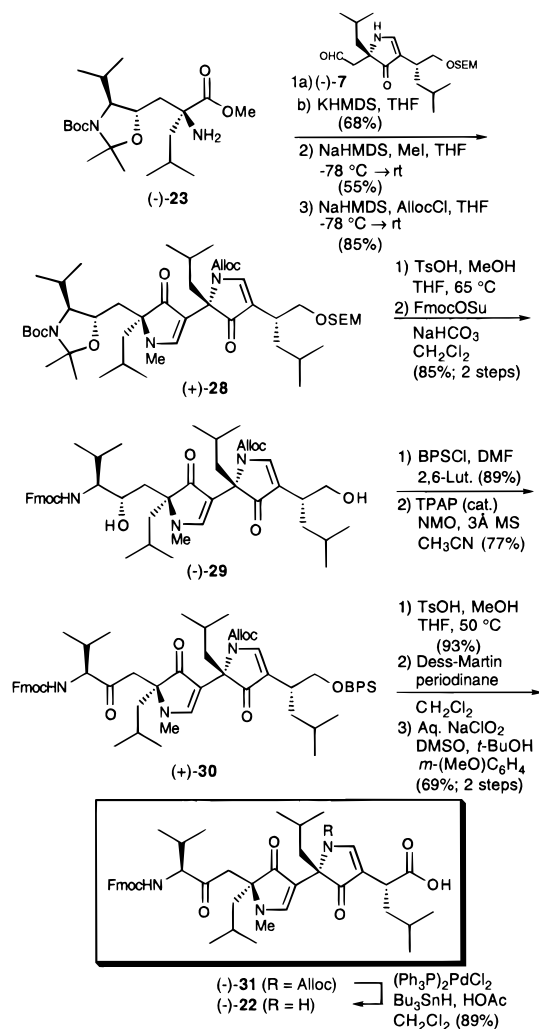
Initially, efforts to oxidize (−)-**29** to the required keto-acid, either in a single operation or in two steps via the keto-aldehyde,

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(30) The binding affinity of the pyrrolinone−peptide hybrid **1** to HLA-DR1 was assessed by using a scintillation proximity assay (SPA) protocol in which an ¹²⁵I-peptide was competitively displaced from HLA-DR1 (isolated from LG2 cells, purified, and coupled to SPA beads via an LB3.1 antibody). See: Ito, K.; Bian, H.-J.; Molina, M.; Han, J. H.; Magram, J.; Saar, E.; Belunis, C.; Bolin, D. R.; Arceo, R.; Campbell, R.; Falcioni, F.; Vidovic, D.; Hammer, J.; Nagy, Z. A. *J. Exp. Med.* **1996**, *183*, 2635.

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(37) Smith, A. B., III; Guzman, M. C.; Favor, D. A.; Berova, N.; Hirschmann, R. Manuscript in preparation.

proved unsuccessful. Ultimately, the desired transformation was accomplished by protecting the primary alcohol with BPSCl and subsequently oxidizing the secondary alcohol with catalytic TPAP[38] and NMO to provide ketone (+)-**30**. Interestingly, TPAP oxidation of the unprotected primary alcohol appeared to afford a keto-aldehyde in which the olefin of the C-terminal pyrrolinone had migrated into conjugation with the aldehyde; this interpretation, however, has not been confirmed. Removal of the BPS group and conversion to the corresponding acid in two steps with Dess−Martin periodinane[26] and buffered aqueous sodium chlorite[39] then gave acid (−)-**31**; the overall yield for the three steps was 64%. Completion of the second generation bispyrrolinone (−)-**22** was achieved via palladium-catalyzed removal of the allyl carbamate.[27] Incorporation of (−)-**22** as a direct replacement for the **VKQN** amino acid sequence in the HA 306−318 peptide, as previously described for ligand **3** (vide supra), provided the second generation hybrid ligand **20**.

Bioassay of Pyrrolinone−Peptide Hybrid Ligand 20. Although hybrid ligand **3** proved to be a competent ligand for the class II MHC HLA-DR1 protein, affinity binding experiments[30] of ligand **20** revealed an IC$_{50}$ of only 1.39 μM. That this ligand, containing the *N*-methyl and isopropyl moieties, was approximately 10 times less potent than the original hybrid ligand **3** was clearly unexpected. Comparison with the control valine peptide PKY**VLLL**TLKLAT (IC$_{50}$ = 78 nM) was even less encouraging. In hindsight, incorporation of both the isopropyl side chain at position 2 and the *N*-methyl pyrrolinone at position 3 in the same analogue prevents a clear determination of their independent roles in disrupting the binding of **20**. The isopropyl side chain might be expected to exert its principal effect upon peptide backbone conformation, decreasing flexibility analogous to the replacement of a glycine by valine in a peptide. However, this modification may also have generated a distorted backbone conformation unanticipated by molecular modeling, resulting in the failure of one or more of the key anchoring groups to bind. Additionally, the decreased flexibility of the backbone might hinder the tight binding of **20** to the MHC protein via induced fit. Alternatively, incorporation of the *N*-methyl pyrrolinone at position 3 may have resulted in unfavorable steric interactions that were not predicted by molecular modeling. The reasons for the decreased affinity of the second generation hybrid ligand (**20**) will become clear, we believe, only upon successful cocrystallization and subsequent crystallographic analysis of the hybrid ligands bound to the class II MHC HLA-DR1 protein.

Summary. The design and synthesis of a competent pyrrolinone−peptide hybrid ligand (**3**) for the class II MHC HLA-DR1 protein has been achieved. The successful construction of this hybrid ligand clearly demonstrates that the pyrrolinone scaffold can be employed to generate high-affinity ligands for non-enzymatic proteins, thereby considerably expanding the scope and utility of this non-peptide scaffold.

Experimental Procedures

General. All reactions were carried out in oven-dried or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent or high-performance liquid chromatography (HPLC) grade. Diethyl ether and tetrahydrofuran (THF) were freshly

distilled from sodium/benzophenone under argon prior to use. Dichloromethane was freshly distilled from calcium hydride before use. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. HPLC grade benzene was purchased from J.T. Baker and stored over 4-Å molecular sieves. Anhydrous *N,N*-dimethylformamide and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium was purchased from Aldrich and standardized by titration with diphenylacetic acid. Water for HPLC was prepared from doubly deionized, filtered water and was purified on a Hydro Services purification unit. Fmoc-protected amino acids were purchased from Bachem or Advanced ChemTech. Fmoc-Thr(*t*-Bu)-Wang resin was obtained from Advanced ChemTech.

Unless otherwise stated, all solution-phase reactions were magnetically stirred and monitored by thin-layer chromatography using 0.25-mm E. Merck precoated silica gel plates. Flash column chromatography was performed with the indicated solvents using silica gel-60 (particle size 0.040−0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Peptide syntheses were carried out either manually or on an Applied Biosystems model 431A peptide synthesizer. HPLC chromatography was performed on an LDC apparatus equipped with two Constametric pumps, a Gradient Master solvent programmer and mixer, and a Spectromonitor III variable-wavelength UV detector. Analytical HPLC was performed in reversed-phase mode using a YMC ODS-AQ column with linear gradients of buffer A (0.05% TFA/H$_2$O) and buffer B (0.04% TFA/CH$_3$CN) at a flow rate of 1.0 mL/min. Preparative HPLC separations were run on a Whatman Magnum 20 partisil 10 ODS-3 column (2 × 50 cm) equipped with a Waters Guard-Pak C$_{18}$ precolumn. For amino acid composition analyses, peptides were hydrolyzed in 6 N HCl with 1 mg of phenol at 115 °C for 22 h in sealed, evacuated hydrolysis tubes. Analyses were performed on a Waters HPLC-based amino acid analysis system using either a Waters Cat Ex resin or a Pierce AA511 column with ninhydrin detection.

Peptides were prepared via solid-phase synthesis procedures using N^α-Fmoc-protected amino acids. The protecting groups for the amino acid side chains were as follows: Lys (Boc), Thr, and Tyr (*t*-Bu ether). All amino acids were coupled using the HBTU/HOBt "FastMoc" protocol. Fmoc protecting groups were removed by treatment with 40% piperidine in DMF for 20 min. Peptides were deblocked and cleaved from the resin by the following method. The peptide resins (∼0.5 g) were treated with 50 μL of dimethyl sulfide, 50 μL of ethanedithiol, 150 μL of anisole, and 5.0 mL of trifluoroacetic acid at room temperature for 2 h. The reaction mixture was filtered, and the spent resin was washed with three 1-mL volumes of trifluoroacetic acid. The combined filtrates were precipitated from 100 mL of ether. The precipitated solid was filtered, washed with three 20-mL volumes of ether, dissolved in 10% aqueous acetic acid, and filtered. The combined aqueous filtrates were then lyophilized to yield the crude product. Purification was carried out by preparative HPLC. The peptides were applied to the column in a minimum volume of either 10−20% HOAc or 0.1% TFA. Gradient elutions were performed using linear gradients of buffer A (0.1% TFA/H$_2$O) and buffer B (0.1% TFA/CH$_3$CN) at a flow rate of 8.0 mL/min with UV detection at 220 nm. Fractions were collected at 1.5−2.5-min intervals, inspected by analytical HPLC, pooled, and lyophilized. Characterization of the final peptides was determined by analytical HPLC and amino acid analysis. The composition values obtained were within acceptable limits. The purified peptides were also analyzed by fast atom bombardment mass spectrometry (FAB-MS) and yielded the expected parent M + H ions within acceptable limits (±1 mass unit).

All melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. The IR and NMR spectra were obtained for CHCl$_3$ and CDCl$_3$ solutions, respectively, unless otherwise noted. Infrared spectra were recorded with a Perkin-Elmer model 283B spectrometer using polystyrene as an external standard. Proton and carbon-13 NMR spectra were recorded on a Bruker AM-500 spectrometer and obtained at 305 K unless otherwise noted. Chemical shifts are reported relative to chloroform (δ 7.24 for proton and δ 77.0 for carbon-13). Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter in the solvent

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(39) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (c) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

indicated. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on either a VG micromass 70/70H high-resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories (Madison, NJ). Single-crystal X-ray diffraction structure determination was performed at the University of Pennsylvania using an Enraf Nonius CAD-4 automated diffractometer.

Oxazolidinone (−)-10. To a mixture of D-leucine (50.0 g, 381 mmol) in absolute ethanol (800 mL) was added a solution of NaOH (15.2 g, 380 mmol) in water (60 mL). The mixture was stirred at room temperature for 90 min, over which time it became homogeneous. The solution was concentrated in vacuo to give a solid mass, and *n*-pentane (1.2 L) was added followed by pivalaldehyde (62.3 mL, 574 mmol). The flask was fitted with a Dean−Stark trap, and the mixture was heated to gentle reflux at 45 °C for 72 h. The heat was then removed, and the mixture was concentrated in vacuo to provide a white solid that was azeotropically dried with toluene (800 mL) and stored under vacuum for 16 h. A suspension of the dried salt in CH_2Cl_2 (1 L) was cooled to 0 °C in an ice bath, benzyl chloroformate (81.6 mL, 572 mmol) was added, and the mixture was stirred at 5 °C for 16 days. Water (400 mL) and a catalytic quantity of (dimethylamino)pyridine (DMAP) were then added while the mixture was still cold. The biphasic system that resulted was warmed to room temperature and stirred for 16 h. The mixture was then extracted with EtOAc (1 L), and the organic phase was washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (1 L each), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using ethyl acetate−hexanes (1:19) as eluant to afford (−)-10 (73.7 g, 58% yield) as a colorless oil: $[\alpha]_D^{23}$ −40.6° (*c* 1.045, CHCl$_3$); IR (CHCl$_3$) 3015 (w), 2955 (s), 1790 (s), 1715 (s), 1390 (m), 1330 (m), 1035 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (m, 5 H), 5.53 (s, 1 H), 5.16 (d, *J* = 11.9 Hz, 1 H), 5.13 (d, *J* = 11.9 Hz, 1 H), 4.31 (apparent t, *J* = 6.6 Hz, 1 H), 1.98 (nonet, *J* = 6.6 Hz, 1 H), 1.77 (ddd, *J* = 13.8, 7.9, 6.4 Hz, 1 H), 1.63 (ddd, *J* = 13.8, 7.9, 6.1 Hz, 1 H), 0.94 (s, 9 H), 0.91 (d, *J* = 3.3 Hz, 3 H), 0.90 (d, *J* = 3.3 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.98, 156.03, 135.25, 128.65, 96.29, 68.36, 55.56, 42.47, 36.94, 25.02, 24.98, 22.73, 21.97; high-resolution mass spectrum (CI, NH$_3$) *m/z* 334.2023 [(M + H)$^+$], calcd for C$_{19}$H$_{28}$NO$_4$ 334.2018.

Anal. Calcd for C$_{19}$H$_{27}$NO$_4$: C, 68.44; H, 8.16. Found: C, 68.52; H, 8.27.

Olefin (+)-11. To a −78 °C solution of (−)-10 (30.0 g, 90.0 mmol) in THF (360 mL) was added 0.5 M KHMDS in toluene (216 mL, 108.0 mmol) at a rate that maintained an internal temperature no higher than −70 °C. The resulting yellow solution was stirred for 15 min, and then freshly distilled allyl bromide (11.7 mL, 135 mmol) was added dropwise via syringe, again maintaining an internal temperature less than −70 °C. The solution was stirred for 15 min at −78 °C and was then quenched at −78 °C by pouring into 10% aqueous NaHSO$_4$ (500 mL). The resulting biphasic mixture was extracted with EtOAc (500 mL), and the organic phase was washed with saturated aqueous NaHCO$_3$ and brine (500 mL each), dried over anhydrous MgSO$_4$, and concentrated in vacuo. The resulting orange oil was purified by flash chromatography using ethyl acetate−hexanes (1:9) as eluant to afford the alkylated oxazolidinone (30.35 g, 90% yield) as a colorless oil: $[\alpha]_D^{23}$ −2.2° (*c* 1.66, CHCl$_3$); IR (CHCl$_3$) 3020 (m), 2965 (m), 1790 (s), 1715 (s), 1330 (s), 1290 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (m, 5 H), 5.44 (m, 2 H), 5.19 (d, *J* = 11.9 Hz, 1 H), 5.05 (apparent t, *J* = 10.5 Hz, 2 H), 4.96 (d, *J* = 17.0 Hz, 1 H), 3.11 (br s, 1 H), 2.42 (apparent ddt, *J* = 13.9, 6.2, 1.3 Hz, 1 H), 2.06 (br s, 1 H), 1.92 (dd, *J* = 14.6, 5.8 Hz, 1 H), 1.85 (dd, *J* = 14.6, 5.2 Hz, 1 H), 0.94 (s, 9 H), 0.93 (d, *J* = 7.2 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.34, 135.16, 130.57, 128.82, 128.63, 121.31, 95.17, 67.81, 67.15, 46.19, 37.97, 25.63, 24.81, 24.59, 23.62; high-resolution mass spectrum (CI, NH$_3$) *m/z* 374.2337 [(M + H)$^+$], calcd for C$_{22}$H$_{32}$NO$_4$ 374.2331.

Anal. Calcd for C$_{22}$H$_{31}$NO$_4$: C, 70.75; H, 8.37. Found: C, 70.67; H, 8.57.

A heterogeneous mixture of the alkylated oxazolidinone (30.35 g, 81.3 mmol) in MeOH and 1 N aqueous NaOH (350 mL each) was heated at reflux for 8 h. The resulting homogeneous solution was cooled

to room temperature and was then concentrated in vacuo to provide a white solid. This solid was then partitioned between EtOAc (700 mL) and 10% aqueous NaHSO$_4$ (1 L). The organic phase was washed with brine (500 mL), dried over anhydrous MgSO$_4$, concentrated in vacuo, and placed under high vacuum for 8 h.

A solution of the crude residue in anhydrous DMF (31 mL) was treated with K$_2$CO$_3$ (31 g) and cooled to 0 °C. Iodomethane (10.2 mL, 163 mmol) was added, and the mixture was stirred and warmed to room temperature for 16 h. The mixture was then diluted with Et$_2$O (800 mL) and was washed with water (4 × 100 mL) followed by brine (200 mL). The organic phase was then dried over anhydrous MgSO$_4$ and concentrated in vacuo to give (+)-11 (24.2 g, 93% yield) as a light yellow oil that was used without further purification. Analytical sample: $[\alpha]_D^{23}$ +27.1° (*c* 2.17, CHCl$_3$); IR (CHCl$_3$) 3425 (m), 3030 (m), 2970 (m), 1730 (s), 1505 (s), 1245 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 5 H), 5.90 (s, 1 H), 5.54 (dddd, *J* = 17.5, 10.3, 7.4, 7.4 Hz, 1 H), 5.08 (d, *J* = 12.8 Hz, 1 H), 5.05 (d, *J* = 12.8 Hz, 1 H), 5.00 (m, 2 H), 3.72 (s, 3 H), 3.11 (dd, *J* = 13.7, 7.1 Hz, 1 H), 2.41 (dd, *J* = 13.9, 7.6 Hz, 1 H), 2.36 (dd, *J* = 14.1, 5.0 Hz, 1 H), 1.66 (dd, *J* = 14.1, 7.6 Hz, 1 H), 1.56 (apparent nonet, *J* = 6.6 Hz, 1 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.25, 153.93, 136.72, 132.15, 128.40, 127.95, 127.86, 118.81, 66.15, 63.51, 52.44, 43.70, 40.73, 24.49, 23.71, 22.49; high-resolution mass spectrum (CI, NH$_3$) *m/z* 320.1861 [(M + H)$^+$], calcd for C$_{18}$H$_{26}$NO$_4$ 320.1862.

Anal. Calcd for C$_{18}$H$_{25}$NO$_4$: C, 67.69; H, 7.89. Found: C, 67.50; H, 8.09.

Acetonides (+)-12a and (−)-12b. To a solution of (+)-11 (152.0 mg, 0.476 mmol) in an 8:1 mixture of acetone and water (13.5 mL) was added *N*-methylmorpholine *N*-oxide (111.5 mg, 0.952 mmol) followed by a catalytic amount of osmium tetroxide. The solution was protected from light, stirred for 16 h, and then quenched by addition of freshly prepared 10% aqueous NaHSO$_3$ (30 mL). The resulting mixture was next extracted with EtOAc (50 mL), the organic phase was washed with brine (50 mL), dried over anhydrous MgSO$_4$, and concentrated in vacuo, and the residue purified by flash chromatography using methanol−methylene chloride (1:19) as eluant to afford the diols (135.5 mg, 81% yield) as a colorless oil consisting of an inseparable mixture of diastereomers that was used without further characterization.

To a solution of the diols (2.20 g, 6.26 mmol) in 2,2-dimethoxypropane (15 mL, 122 mmol) was added a catalytic amount of *p*-TsOH. The solution was stirred at room temperature for 2 h and was then diluted with Et$_2$O (100 mL). The resulting mixture was washed with saturated aqueous NaHCO$_3$ followed by brine (50 mL each). The organic phase was then dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using ethyl acetate−hexanes (1:4) as eluant to give (+)-12a (*R$_f$* 0.45, 1.16 g) and (−)-12b (*R$_f$* 0.38, 874 mg) in 83% combined yield.

Acetonide (+)-12a: $[\alpha]_D^{23}$ +27.2° (*c* 2.405, CHCl$_3$); IR (CHCl$_3$) 3405 (m), 3000 (m), 2950 (m), 1720 (s), 1500 (s), 1240 (s), 1060 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 5 H), 6.14 (s, 1 H), 5.07 (d, *J* = 12.4 Hz, 1 H), 5.04 (d, *J* = 12.4 Hz, 1 H), 3.98 (m, 2 H), 3.71 (s, 3 H), 3.44 (apparent t, *J* = 6.7 Hz, 1 H), 2.57 (dd, *J* = 14.0, 2.9 Hz, 1 H), 2.33 (dd, *J* = 14.2, 5.7 Hz, 1 H), 2.01 (dd, *J* = 14.0, 9.2 Hz, 1 H), 1.62 (dd, *J* = 14.4, 6.9, 1 H), 1.50 (apparent septet, *J* = 6.6 Hz, 1 H), 1.29 (s, 3 H), 1.24 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.42, 153.98, 136.61, 128.43, 128.03, 127.87, 108.90, 71.65, 69.21, 66.25, 61.50, 52.40, 44.09, 41.00, 26.61, 25.48, 24.40, 23.64, 22.83; high-resolution mass spectrum (CI, NH$_3$) *m/z* 394.2242 [(M + H)$^+$], calcd for C$_{21}$H$_{32}$NO$_6$ 394.2229.

Anal. Calcd for C$_{21}$H$_{31}$NO$_6$: C, 64.10; H, 7.94. Found: C, 64.31; H, 7.97.

Acetonide (−)-12b: $[\alpha]_D^{23}$ −0.9° (*c* 0.82, CHCl$_3$); IR (CHCl$_3$) 3415 (m), 3015 (m), 2960 (s), 1725 (s), 1500 (s), 1240 (s), 1065 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 5 H), 5.88 (s, 1 H), 5.06 (apparent s, 2 H), 3.95 (m, 1 H), 3.89 (dd, *J* = 7.7, 6.1 Hz, 1 H), 3.73 (s, 3 H), 3.39 (apparent t, *J* = 7.6 Hz, 1 H), 2.62 (dd, *J* = 14.3, 7.0 Hz, 1 H), 2.26 (dd, *J* = 13.9, 5.1 Hz, 1 H), 1.96 (dd, *J* = 14.5, 4.4 Hz, 1 H), 1.74 (dd, *J* = 14.1, 7.0 Hz, 1 H), 1.59 (m, 1 H), 1.30 (s, 3 H), 1.27 (s, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 174.39, 154.34, 136.74, 128.46, 128.01, 127.95, 108.91, 72.64, 69.32, 66.27, 62.01, 52.51, 44.35, 39.43, 26.62, 25.79, 24.22, 23.79, 22.82; high-resolution mass spectrum (CI, NH$_3$) *m/z* 394.2236 [(M + H)$^+$], calcd for C$_{21}$H$_{32}$NO$_6$ 394.2229.

Anal. Calcd for C$_{21}$H$_{31}$NO$_6$: C, 64.10; H, 7.94. Found: C, 63.80; H, 7.96.

Amino Ester (−)-6. To a mixture of (+)-**12a** (5.0341 g, 12.9 mmol) and 10% Pd/C (1.0 g) in absolute EtOH (51 mL) was added freshly distilled cyclohexene (10.56 g, 128.6 mmol). The mixture was then heated at reflux for 15 min, cooled to room temperature, filtered, and concentrated in vacuo. The residue was further purified by adding CHCl$_3$ (100 mL), filtering the resulting suspension, and then concentrating the clear solution in vacuo. This procedure gave (−)-**6** (3.2899 g, 99% yield) as a colorless oil that was used without further purification. Analytical sample: [α]$_D^{23}$ −1.3° (*c* 1.015, CHCl$_3$); IR (CHCl$_3$) 2955 (s), 1760 (s), 1380 (m), 1370 (m), 1225 (s), 1155 (m), 1135 (m), 1065 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.19 (dddd, *J* = 8.8, 6.9, 6.1, 4.1 Hz, 1 H), 4.05 (dd *J* = 8.0, 6.1 Hz, 1 H), 3.67 (s, 3 H), 3.50 (dd, *J* = 7.9, 7.1 Hz, 1 H), 2.12 (dd *J* = 13.9, 8.8 Hz, 1 H), 1.73 (dd, *J* = 13.4, 7.4 Hz, 1 H), 1.65 (dd, *J* = 13.9, 4.1 Hz, 1 H), 1.64 (m, 3 H), 1.48 (dd, *J* = 13.4, 4.4 Hz, 1 H), 1.33 (s, 3 H), 1.29 (s, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.81 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.63, 108.92, 71.98, 70.01, 59.11, 51.93, 49.53, 45.32, 26.69, 25.64, 24.74, 24.11, 23.01; high-resolution mass spectrum (CI, NH$_3$) *m/z* 260.1873 [(M + H)$^+$], calcd for C$_{13}$H$_{26}$NO$_4$ 260.1862.

Olefin (+)-13. In a procedure analogous to the preparation of (+)-**11**, a −78 °C solution of (−)-**10** (37.6 g, 113 mmol) in THF (450 mL) was treated with 0.5 M KHMDS in toluene (271 mL, 136 mmol) followed by freshly distilled prenyl bromide (19.5 mL, 169 mmol). Workup and flash chromatography using ethyl acetate−hexanes (1:9) as eluant then afforded the alkylated oxazolidinone (42.58 g, 94% yield) as a colorless oil: [α]$_D^{23}$ +32.3° (*c* 7.95, CHCl$_3$); IR (CHCl$_3$) 3020 (m), 2960 (m), 1790 (s), 1710 (s), 1325 (s), 1185 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33 (m, 5 H), 5.40 (s, 1 H), 5.21 (d, *J* = 12.0 Hz, 1 H), 5.01 (d, *J* = 12.0 Hz, 1 H), 4.73 (apparent t, *J* = 7.6 Hz, 1 H), 3.04 (br s, 1 H), 2.41 (dd, *J* = 14.6, 6.9 Hz, 1 H), 2.10 (br s, 1 H), 1.92 (dd, *J* = 14.6, 5.8 Hz, 1 H), 1.85 (dd, *J* = 14.6, 5.2 Hz, 1 H), 1.60 (s, 3 H), 1.51 (s, 3 H), 0.94 (s, 9 H), 0.92 (apparent t, *J* = 7.1 Hz, 7H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.67, 137.79, 135.31, 128.57, 128.54, 128.49, 115.94, 95.13, 67.68, 67.42, 46.16, 37.94, 26.03, 25.66, 24.81, 24.59, 23.68, 17.99; high-resolution mass spectrum (CI, NH$_3$) *m/z* 402.2639 [(M + H)$^+$], calcd for C$_{24}$H$_{36}$NO$_4$ 402.2644.

Anal. Calcd for C$_{24}$H$_{35}$NO$_4$: C, 71.79; H, 8.79. Found: C, 71.54; H, 8.86.

In a procedure analogous to the preparation of (+)-**11**, a heterogeneous mixture of the alkylated oxazolidinone (42.58 g, 106 mmol) in MeOH and 1 N aqueous NaOH (350 mL each) was heated at reflux for 8 h. The resulting homogeneous solution was worked up, and a 0 °C solution of the crude residue in anhydrous DMF (43 mL) was treated with K$_2$CO$_3$ (43 g) and iodomethane (13.2 mL, 212 mmol). The mixture was stirred and warmed to room temperature over 16 h and was then worked up and concentrated in vacuo to give (+)-**13** (33.16 g, 90% yield for two steps) as a light yellow oil that was used without further purification. Analytical sample: [α]$_D^{23}$ +39.0° (*c* 1.655, CHCl$_3$); IR (CHCl$_3$) 3420 (m), 3020 (m), 2960 (m), 1720 (s), 1500 (s), 1235 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30 (m, 5 H), 5.88 (s, 1 H), 5.07 (d, *J* = 12.5 Hz, 1 H), 5.04 (d, *J* = 12.5 Hz, 1 H), 4.85 (apparent t, *J* = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.02 (dd, *J* = 14.3, 7.4 Hz, 1 H), 2.39 (m, 2 H), 1.67 (dd, *J* = 14.1, 7.7, 1 H), 1.62 (s, 3 H), 1.55 (m, 1 H), 1.50 (m, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.68, 153.96, 136.84, 135.64, 128.43, 127.94, 117.62, 66.10, 63.65, 52.36, 43.77, 35.43, 25.91, 24.57, 23.79, 22.50, 17.72; high-resolution mass spectrum (CI, NH$_3$) *m/z* 348.2182 [(M + H)$^+$], calcd for C$_{20}$H$_{30}$NO$_4$ 348.2174.

Anal. Calcd for C$_{20}$H$_{29}$NO$_4$: C, 69.14; H, 8.41. Found: C, 68.98; H, 8.25.

Amino Ester (−)-8. A −78 °C solution of (+)-**13** (1.00 g, 2.88 mmol) in CH$_2$Cl$_2$ (32 mL) was saturated with ozone until a blue color persisted. The solution was then purged with argon until the blue color dissipated; Ph$_3$P (1.13 g, 4.31 mmol) was then added. The resulting solution was stirred and warmed to room temperature under argon for

16 h. The solution was then concentrated in vacuo and the resulting white solid purified by flash chromatography using ethyl acetate−hexanes (1:4) as eluant to yield the aldehyde (904.5 mg, 98% yield) as a light yellow oil: [α]$_D^{23}$ +5.8° (*c* 1.670, CHCl$_3$); IR (CHCl$_3$) 3410 (m), 3020 (m), 2975 (m), 1740 (s), 1725 (s), 1500 (s), 1240 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.58 (s, 1 H), 7.31 (m, 5 H), 6.06 (s, 1 H), 5.07 (d, *J* = 12.3 Hz, 1 H), 5.00 (d, *J* = 12.3 Hz, 1 H), 3.74 (s, 3 H), 3.71 (d, *J* = 17.9 Hz, 1 H), 2.90 (d, *J* = 17.9, 1 H), 2.34 (m, 1 H), 1.55 (m, 2 H), 0.85 (d, *J* = 6.3 Hz, 3 H), 0.77 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.91, 173.25, 154.18, 136.34, 128.45, 128.06, 127.82, 66.42, 59.53, 52.85, 49.79, 44.03, 23.88, 23.62, 23.07; high-resolution mass spectrum (CI, NH$_3$) *m/z* 322.1659 [(M + H)$^+$], calcd for C$_{17}$H$_{24}$NO$_5$ 322.1654.

To a solution of the aldehyde (8.80 g, 27.4 mmol) in MeOH (24 mL) was added trimethyl orthoformate (24 mL, 219 mmol) and a catalytic quantity of *p*-TsOH. The solution was heated at reflux with stirring for 2 h and was then diluted with Et$_2$O (300 mL). The mixture was washed with saturated aqueous NaHCO$_3$ and brine (100 mL each), and the organic phase was then dried over anhydrous MgSO$_4$ and concentrated in vacuo. Flash chromatography using ethyl acetate−hexanes (1:4) as eluant then afforded the dimethyl acetal (9.47 g, 94% yield) as a pale yellow oil: [α]$_D^{23}$ +13.0° (*c* 1.625, CHCl$_3$); IR (CHCl$_3$) 3410 (m), 3005 (m), 2955 (m), 1720 (s), 1495 (s), 1235 (s), 1050 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (m, 5 H), 6.06 (s, 1 H), 5.08 (d, *J* = 12.4 Hz, 1 H), 5.05 (d, *J* = 12.4 Hz, 1 H), 4.20 (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.70 (s, 3 H), 3.21 (s, 3 H), 3.20 (s, 3 H), 2.67 (dd, *J* = 14.1, 2.6 Hz, 1 H), 2.32 (dd, *J* = 14.2, 5.6 Hz, 1 H), 2.06 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.62 (dd, *J* = 14.2, 7.0 Hz, 1 H), 1.50 (apparent nonet, *J* = 6.7 Hz, 1 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.43, 153.91, 136.75, 128.45, 128.03, 127.99, 102.50, 66.24, 60.92, 55.07, 53.34, 52.37, 43.81, 39.87, 24.32, 23.72, 22.84; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) *m/z* 390.1899 [(M + Na)$^+$], calcd for C$_{19}$H$_{29}$NO$_6$Na 390.1893.

Anal. Calcd for C$_{19}$H$_{29}$NO$_6$: C, 62.11; H, 7.96. Found: C, 62.19; H, 7.74.

In a procedure analogous to the preparation of (−)-**6**, a mixture of the dimethyl acetal (13.1 g, 36.9 mmol), 10% Pd/C (2.6 g), and freshly distilled cyclohexene (30.3 g, 369 mmol) in absolute EtOH (147 mL) was heated at reflux for 15 min. The mixture was then filtered and concentrated in vacuo to give (−)-**8** (8.10 g, 99% yield) as a light yellow oil that was used without further purification. Analytical sample: [α]$_D^{23}$ −22.7° (*c* 2.37, CHCl$_3$); IR (CHCl$_3$) 3680 (w), 3380 (w), 3000 (m), 2955 (s), 1760 (s), 1225 (m), 1195 (m), 1125 (s), 1075 (m), 1045 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.37 (apparent t, *J* = 5.6 Hz, 1 H), 3.64 (s, 3 H), 3.26 (s, 3 H), 3.23 (s, 3 H), 2.05 (dd, *J* = 14.1, 5.6 Hz, 1 H), 1.86 (br s, 2 H), 1.77 (dd, *J* = 14.1, 5.6 Hz, 1 H), 1.65 (m, 2 H), 1.46 (m, 1 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.77 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.79, 102.38, 58.69, 53.32, 53.23, 51.81, 49.72, 43.47, 24.69, 23.82, 22.77; high-resolution mass spectrum (CI, NH$_3$) *m/z* 234.1707 [(M + H)$^+$], calcd for C$_{11}$H$_{24}$NO$_4$ 234.1705.

Anal. Calcd for C$_{11}$H$_{23}$NO$_4$: C, 56.63; H, 9.94. Found: C, 56.40; H, 10.16.

Aldehyde (+)-9. To a 0 °C solution of (*R*)-5-methyl-2-(2-methylpropyl)-4-hexen-1-ol^{4e} (245.7 mg, 1.44 mmol) in CH$_2$Cl$_2$ (0.72 mL) was added diisopropylethylamine (932 mg, 7.21 mmol) followed by trimethylsilylethoxymethyl chloride (SEMCl; 722 mg, 4.33 mmol). The resultant red solution was stirred for 20 min at room temperature and was then diluted with Et$_2$O (30 mL). This solution was then washed with water (30 mL), and the organic phase was dried over anhydrous MgSO$_4$ and concentrated in vacuo. The residue was then purified by flash chromatography using ethyl acetate−hexanes (1:49) as eluant to provide the SEM ether (376.2 mg, 87% yield) as a colorless oil: [α]$_D^{23}$ −0.2° (*c* 1.75, CHCl$_3$); IR 3015 (m), 2965 (s), 2935 (s), 1255 (m), 1060 (s), 1030 (s), 860 (s), 835 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.09 (apparent tt, *J* = 7.3, 1.4 Hz, 1 H), 4.61 (s, 2 H), 3.59 (m, 2 H), 3.36 (apparent dq, *J* = 9.5, 5.7 Hz, 2 H), 1.99 (apparent dsept, *J* = 7.1, 7.1 Hz, 2 H), 1.66 (s, 3 H), 1.64 (m, 2 H), 1.57 (s, 3 H), 1.13 (m, 2 H), 0.90 (m, 2 H), 0.85 (d, *J* = 6.6, 6 H), −0.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 132.27, 122.59, 95.01, 70.68, 64.83,

40.85, 36.75, 30.03, 25.80, 25.72, 25.34, 22.87, 18.14, 17.75, −1.45; high-resolution mass spectrum (CI, NH$_3$) m/z 318.2823 [(M + NH$_4$)$^+$], calcd for C$_{17}$H$_{40}$NO$_2$Si 318.2828.

In a procedure analogous to the preparation of (−)-**8**, ozonolysis of a −78 °C solution of the SEM ether (12.10 g, 40.3 mmol) in CH$_2$Cl$_2$ (370 mL) followed by treatment with Ph$_3$P (13.20 g, 50.3 mmol) gave (+)-**9** (8.18 g, 74% yield) as a light yellow oil after workup and flash chromatography using ethyl acetate−hexanes (1:19) as eluant: [α]$_D^{23}$ +15.8° (*c* 1.56, CHCl$_3$); IR 3000 (m), 2960 (s), 1725 (s), 1250 (m), 1055 (s), 1030 (s), 855 (s), 830 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.74 (dd, J = 2.5, 1.9 Hz, 1 H), 4.60 (d, J = 6.7 Hz, 1 H), 4.58 (d, J = 6.7 Hz, 1 H), 3.55 (apparent dt, J = 8.4, 1.6 Hz, 2 H), 3.52 (dd, J = 9.6, 4.2 Hz, 1 H), 3.32 (dd, J = 9.6, 7.2 Hz, 1 H), 2.42 (m, 1 H), 2.31 (m, 2 H), 1.60 (m, 1 H), 1.18 (m, 2 H), 0.90 (m, 2 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), −0.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.34, 94.88, 70.68, 65.13, 47.17, 40.96, 31.92, 25.26, 22.71, 22.59, 18.11, −1.45; high-resolution mass spectrum (CI, NH$_3$) m/z 292.2302 [(M + NH$_4$)$^+$], calcd for C$_{14}$H$_{34}$NO$_3$Si 292.2308.

Aldehyde (−)-7. To a solution of (−)-**8** (6.60 g, 29.8 mmol) in benzene (31 mL) was added a solution of (+)-**9** (8.18 g, 29.8 mmol) in benzene (31 mL). Condensation was effected by allowing the solution to stir for 20 min and then allowing it to stand undisturbed for 2 h. The highly turbid mixture was concentrated in vacuo, and the residue was azeotropically dehydrated with additional benzene (7 × 62 mL).

To a solution of the residue in THF (310 mL) was added 0.5 M KHMDS in toluene (238 mL, 119 mmol) rapidly via addition funnel. The resulting dark amber solution was stirred for 15 min, quenched by addition of 10% aqueous NaHSO$_4$ (300 mL), and diluted with EtOAc (600 mL). The mixture was then washed with saturated aqueous NaHCO$_3$ followed by brine (500 mL each). The organic phase was next dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using ethyl acetate−hexanes (2:3) as eluant to give the monopyrrolinone (10.64 g, 78% yield) as a yellow oil: [α]$_D^{23}$ +36.8° (*c* 1.295, CHCl$_3$); IR 3425 (w), 3005 (m), 2960 (s), 1665 (m), 1585 (m), 1250 (m), 1120 (m), 1060 (s), 860 (m), 835 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, J = 3.8 Hz, 1 H), 5.64 (d, J = 3.5 Hz, 1 H), 4.59 (d, J = 6.6 Hz, 1 H), 4.57 (d, J = 6.6 Hz, 1 H), 4.42 (dd, J = 7.2, 4.3 Hz, 1 H), 3.55 (m, 3 H), 3.42 (dd, J = 9.4, 5.9 Hz, 1 H), 3.31 (s, 3 H), 3.25 (s, 3 H), 2.72 (dddd, J = 9.2, 5.8, 5.8, 5.8 Hz, 1 H), 1.88 (dd, J = 14.4, 4.3 Hz, 1 H), 1.61 (m, 2 H), 1.48 (m, 3 H), 1.39 (m, 2 H), 0.89 (m, 2 H), 0.84 (d, J = 2.2 Hz, 3 H), 0.83 (d, J = 2.2 Hz, 3 H), 0.81 (d, J = 6.3 Hz, 3 H), 0.77 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.83, 161.31, 114.56, 102.45, 95.01, 70.88, 67.98, 64.90, 53.98, 53.36, 43.63, 40.49, 40.31, 31.81, 25.57, 24.30, 24.26, 24.18, 23.29, 22.07, 18.07, −1.45; high-resolution mass spectrum (CI, NH$_3$) m/z 458.3323 [(M + H)$^+$], calcd for C$_{24}$H$_{48}$NO$_5$Si 458.3301.

Anal. Calcd for C$_{24}$H$_{47}$NO$_5$Si: C, 62.98; H, 10.35. Found: C, 62.79; H, 10.28.

To a solution of the monopyrrolinone (1.5074 g, 3.29 mmol) in a 3:1 mixture of THF and water (60 mL) was added *p*-TsOH (627 mg, 330 mmol). The solution was heated at 55 °C for 3 h and was then cooled to room temperature and diluted with Et$_2$O (200 mL). The mixture was washed with saturated aqueous NaHCO$_3$ and brine (100 mL each). The organic phase was then dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using methanol−methylene chloride (1:24) as eluant to provide (−)-**7** (1.0780 g, 80% yield) as a yellow oil: [α]$_D^{23}$ −49.5° (*c* 1.275, CHCl$_3$); IR (CHCl$_3$) 3460 (w), 3020 (m), 2970 (s), 1665 (s), 1585 (m), 1255 (s), 1060 (s), 1030 (s), 860 (s), 835 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.55 (d, J = 2.8 Hz, 1 H), 7.79 (d, J = 3.8 Hz, 1 H), 5.65 (br d, J = 3.2 Hz, 1 H), 4.59 (apparent s, 2 H), 3.56 (m, 3 H), 3.44 (dd, J = 9.4, 5.5 Hz, 1 H), 2.72 (m, 2 H), 2.54 (d, J = 16.6 Hz, 1 H), 1.69 (dd, J = 14.0, 5.5 Hz, 1 H), 1.63 (dd, J = 14.0, 6.8 Hz, 1 H), 1.54 (m, 1 H), 1.46 (m, 1 H), 1.39 (m, 2 H), 0.90 (apparent dd, J = 9.1, 7.7 Hz, 2 H), 0.85 (m, 9 H), 0.78 (d, J = 6.6 Hz, 3 H), −0.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.51, 200.25, 161.01, 114.33, 95.01, 70.58, 67.42, 65.00, 50.52, 44.41, 40.35, 31.84, 25.61, 24.31, 24.27, 23.76, 23.21, 22.09, 18.10, −1.42; high-resolution mass spectrum (CI, NH$_3$) m/z 412.2876 [(M + H)$^+$], calcd for C$_{22}$H$_{41}$NO$_4$Si 412.2883.

Anal. Calcd for C$_{22}$H$_{40}$NO$_4$Si: C, 64.19; H, 10.04. Found: C, 63.90; H, 10.12.

Bispyrrolinone (+)-15. To a solution of (−)-**7** (3.4555 g, 13.4 mmol) in benzene (13.5 mL) was added a solution of (−)-**6** (5.5285 g, 13.4 mmol) in benzene (13.5 mL). Condensation was effected by allowing the solution to stir for 20 min and then by allowing it to stand undisturbed for 2 h. The highly turbid mixture was concentrated in vacuo, and the residue was azeotropically dehydrated with additional benzene (7 × 27 mL).

To a solution of the residue in THF (134 mL) was added 0.5 M KHMDS in toluene (121 mL, 60.5 mmol) rapidly via addition funnel. The resulting dark amber solution was stirred for 15 min, quenched by addition of 10% aqueous NaHSO$_4$ (200 mL), and extracted with EtOAc (400 mL). The mixture was then washed with saturated aqueous NaHCO$_3$ followed by brine (300 mL each); the organic phase was dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using methanol−methylene chloride (3:97) as eluant to give the bispyrrolinone (6.3474 g, 76% yield) as a yellow oil: [α]$_D^{23}$ −165.6° (*c* 0.215, CHCl$_3$); IR (CHCl$_3$) 3435 (w), 2970 (s), 2880 (s), 1740 (s), 1655 (m), 1585 (m), 1380 (s), 1255 (s), 1050 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, J = 4.1 Hz, 1 H), 7.76 (d, J = 3.8 Hz, 1 H), 6.96 (d, J = 3.7 Hz, 1 H), 6.23 (d, J = 4.0 Hz, 1 H), 4.58 (s, 2 H), 4.33 (dddd, J = 10.0, 6.6, 6.6, 3.0 Hz, 1 H), 4.03 (dd, J = 8.1, 6.0 Hz, 1 H), 3.55 (apparent dt, J = 8.0, 1.1 Hz, 2 H), 3.51 (dd, J = 9.4, 5.0 Hz, 1 H), 3.43 (m, 2 H), 2.74 (m, 1 H), 1.84 (m, 1 H), 1.79 (dd, J = 14.2, 3.0 Hz, 1 H), 1.67 (dd, J = 13.9, 5.9 Hz, 1 H), 1.57 (m, 3 H), 1.43 (dd, J = 14.2, 10.5 Hz, 1 H), 1.36 (s, 3 H), 1.33 (m, 4 H), 1.32 (s, 3 H), 0.89 (m, 2 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.79 (m, 9 H), 0.73 (d, J = 6.9 Hz, 3 H), 0.65 (d, J = 6.6 Hz, 3 H), −0.02 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.29, 202.98, 161.96, 160.63, 113.49, 110.47, 109.51, 94.97, 72.26, 71.35, 70.00, 69.65, 67.62, 64.88, 47.24, 42.34, 41.39, 40.73, 31.34, 26.97, 25.62, 25.58, 24.84, 24.46, 24.12, 24.10, 23.95, 23.71, 23.51, 21.83, 18.08, −1.43; high-resolution mass spectrum (CI, NH$_3$) m/z 621.4315 [(M + H)$^+$], calcd for C$_{34}$H$_{61}$N$_2$O$_6$Si 621.4298.

To a −78 °C solution of the bispyrrolinone (794.4 mg, 1.28 mmol) in THF (13 mL) was added 1.0 M NaHMDS in THF (3.84 mL, 3.84 mmol). The solution was stirred for 10 min, allyl chloroformate (616.8 mg, 5.12 mmol) was added dropwise via syringe, and the solution was stirred for 30 min. The solution was then poured into 10% aqueous NaHSO$_4$ (50 mL) and diluted with EtOAc (100 mL). The resulting mixture was washed with saturated aqueous NaHCO$_3$ followed by brine (50 mL). The organic phase was then dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using ethyl acetate−hexanes (1:4) as eluant to provide (+)-**15** (894.9 mg, 89% yield) as a light yellow oil: [α]$_D^{23}$ +80.6° (*c* 1.27, CHCl$_3$); IR (CHCl$_3$) 2960 (m), 1730 (s), 1705 (s), 1610 (m), 1400 (s), 1230 (s), 1060 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.39 (br m, 2 H), 5.91 (br m, 2 H), 5.32 (br m, 4 H), 4.64 (br m, 7 H), 3.81 (br s, 1 H), 3.53 (br m, 5 H), 2.79 (br s, 1 H), 2.38 (br dd, J = 13.2, 5.4 Hz, 1 H), 2.14 (br m, 2 H), 1.60 (br m, 2 H), 1.43 (br m, 2 H), 1.28 (br s, 3 H), 1.24 (br s, 7 H), 0.91 (apparent t, J = 9.7 Hz, 2 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.82 (br m, 6 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.72 (d, J = 6.6 Hz, 3 H), 0.59 (br m, 3 H), −0.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.80, 155.36, 154.52, 154.16, 148.48, 131.81, 131.42, 123.44, 120.43, 119.89, 118.84, 107.63, 95.02, 71.43, 71.14, 69.86, 69.08, 67.73, 67.29, 66.87, 65.09, 45.36, 44.50, 42.08, 41.40, 40.26, 40.09, 31.80, 29.67, 26.54, 25.91, 25.63, 25.19, 24.29, 23.73, 23.48, 23.26, 23.12, 22.14, 18.12, −1.42; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) m/z 811.4532 [(M + Na)$^+$], calcd for C$_{42}$H$_{68}$N$_2$O$_{10}$SiNa 811.4541.

Anal. Calcd for C$_{42}$H$_{68}$N$_2$O$_{10}$Si: C, 63.93; H, 8.69. Found: C, 64.01; H, 8.73.

Tosylate (+)-16. To a solution of (+)-**15** (7.6385 g, 9.68 mmol) in HOAc (230 mL) and MeOH (76 mL) was added a catalytic amount of *p*-TsOH. The solution was stirred at 35 °C and carefully monitored by TLC analysis using ethyl acetate−hexanes (1:1) as eluant until most of the starting material had been consumed (ca. 45 min). The solution was cooled and was then diluted with EtOAc (500 mL). The resultant mixture was carefully washed with saturated aqueous NaHCO$_3$ (4 × 300 mL, or until basic to litmus) and brine (300 mL). The organic phase was then dried over anhydrous MgSO$_4$ and concentrated in vacuo.

Purification of the residue by flash chromatography using ethyl acetate−hexanes (11:9) as eluant, followed by resubjection of the recovered starting material to the reaction conditions, gave the diol (5.4933 g, 76% overall yield) as a light yellow oil: $[\alpha]_D^{23}$ +143.4° (*c* 1.585, CHCl$_3$); IR (CHCl$_3$) 3510 (w), 3020 (m), 2970 (m), 1710 (s), 1610 (m), 1405 (s), 1255 (s), 1235 (s), 1060 (m), 1040 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.42 (br m, 2 H), 5.92 (br m, 2 H), 5.31 (br m, 4 H), 4.67 (br m, 7 H), 3.53 (br m, 5 H), 3.31 (br m, 3 H), 2.90 (br d, *J* = 4.8 Hz, 1 H), 2.77 (br m, 1 H), 2.35 (dd, *J* = 13.5, 5.6 Hz, 1 H), 2.13 (br m, 1 H), 2.03 (br m, 1 H), 1.84 (br m, 1 H), 1.63 (br m, 1 H), 1.53 (br m, 1 H), 1.41 (br m, 3 H), 1.19 (br m, 1 H), 0.89 (apparent t, *J* = 8.3 Hz, 2 H), 0.81 (br m, 12 H), 0.70 (d, *J* = 6.6 Hz, 3 H), 0.59 (br m, 3 H), −0.02 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.65, 154.27, 149.73, 131.57, 131.38, 124.06, 119.95, 119.20, 94.96, 71.87, 69.83, 67.98, 67.44, 66.87, 66.48, 65.09, 44.79, 42.79, 41.78, 40.34, 40.11, 31.71, 25.15, 24.19, 23.79, 23.72, 23.23, 23.12, 22.05, 18.08, −1.44; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) *m/z* 771.4236 [(M + Na)$^+$], calcd for C$_{39}$H$_{64}$N$_2$O$_{10}$SiNa 771.4228.

Anal. Calcd for C$_{39}$H$_{64}$N$_2$O$_{10}$Si: C, 62.54; H, 8.61. Found: C, 62.67; H, 8.42.

To a 0 °C solution of the diol (8.7000 g, 11.6 mmol) and triethylamine (5.9 g, 58.3 mmol) in CH$_2$Cl$_2$ (58 mL) was added TsCl (2.6694 g, 14.0 mmol). The solution was stirred for 30 min and was then cooled to 5 °C for 16 h. The solution was then diluted with EtOAc (400 mL), and the resulting mixture was washed with 10% aqueous NaHSO$_4$, saturated aqueous NaHCO$_3$, and brine (200 mL each). The organic phase was then dried over anhydrous MgSO$_4$ and concentrated in vacuo. Purification of the residue by gradient flash chromatography using ethyl acetate−hexanes (1:4 then 3:1) as eluant, followed by resubjection of the recovered starting material to the reaction conditions, gave (+)-**16** (9.2210 g, 87% overall yield) as a light yellow oil: $[\alpha]_D^{23}$ +98.8° (*c* 1.235, CHCl$_3$); IR (CHCl$_3$) 3520 (w), 3020 (m), 2965 (m), 1710 (s), 1610 (m), 1405 (s), 1255 (m), 1230 (m), 1180 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.41 (br m, 2 H), 7.73 (br d, *J* = 7.7 Hz, 2 H), 7.30 (br d, *J* = 7.9 Hz, 2 H), 5.90 (br m, 2 H), 5.33 (br m, 4 H), 4.72 (br s, 2 H), 4.58 (br m, 5 H), 3.72 (br m, 2 H), 3.53 (br m, 5 H), 2.75 (br m, 2 H), 2.41 (s 3 H), 2.35 (br m, 1 H), 2.20 (br d, *J* = 14.2 Hz, 1 H), 2.02 (br m, 1 H), 1.78 (br dd, *J* = 14.1, 9.5 Hz, 1 H), 1.57 (br m, 2 H), 1.41 (br m, 3 H), 1.19 (br m, 1 H), 0.90 (apparent t, *J* = 8.3 Hz, 2 H), 0.85 (d *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.7 Hz, 3 H), 0.70 (d, *J* = 6.6 Hz, 3 H), 0.58 (br d, *J* = 6.5 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.72, 199.41, 155.48, 154.20, 150.42, 149.59, 144.80, 132.83, 131.61, 129.81, 127.99, 124.04, 120.11, 119.76, 119.30, 94.99, 72.85, 69.88, 67.85, 67.37, 65.09, 64.54, 44.67, 42.50, 41.32, 40.36, 31.72, 25.13, 24.25, 24.18, 23.79, 23.66, 23.21, 23.16, 22.04, 21.60, 18.10, −1.43; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) *m/z* 925.4319 [(M + Na)$^+$], calcd for C$_{46}$H$_{70}$N$_2$O$_{12}$SSiNa 925.4317.

Anal. Calcd for C$_{46}$H$_{70}$N$_2$O$_{12}$SSi: C, 61.17; H, 7.81. Found: C, 61.44; H, 7.78.

Azide (+)-17. To a solution of (+)-**16** (39.4 mg, 0.044 mmol) in benzene (1 mL) was added tetrabutylammonium bromide (141 mg, 0.437 mmol). The solution was heated to 65 °C and was stirred for 90 min. The resulting solution was then concentrated in vacuo and purified by flash chromatography using ethyl acetate−hexanes (1:4) as eluant to provide the bromide (32.4 mg, 92% yield) as a colorless oil: $[\alpha]_D^{23}$ +103.3° (*c* 3.185, CHCl$_3$); IR (CHCl$_3$) 3510 (w), 3010 (w), 2960 (m), 1705 (s), 1610 (m), 1400 (s), 1250 (m), 1220 (m), 1060 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.42 (br m, 2 H), 5.92 (br m, 2 H), 5.31 (br m, 4 H), 4.68 (br m, 4 H), 4.58 (br s, 3 H), 3.53 (br m, 2 H), 3.20 (br m, 2 H), 2.78 (br m, 2 H), 2.38 (br m, 1 H), 2.03 (br m, 1 H), 1.94 (br m, 1 H), 1.68 (br m, 1 H), 1.57 (br m, 1 H), 1.43 (br m, 3 H), 1.21 (br m, 2 H), 0.89 (apparent t, *J* = 8.3 Hz, 2 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H), 0.71 (d, *J* = 6.6 Hz, 3 H), 0.60 (br d, *J* = 6.5 Hz, 3 H), −0.02 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.87, 199.59, 155.45, 154.22, 150.49, 149.44, 131.67, 131.47, 123.96, 120.22, 119.75, 119.21, 94.96, 71.49, 69.86, 67.78, 67.33, 66.51, 65.07, 45.71, 44.68, 43.31, 42.33, 40.30, 40.08, 38.98, 31.72, 29.64, 25.11, 24.25, 23.19, 23.15, 22.04, 18.08, −1.44; high-resolution mass spectrum (FAB,

p-nitrobenzyl alcohol) *m/z* 833.3380 [(M + Na)$^+$], calcd for C$_{39}$H$_{63}$N$_2$O$_9$-BrSiNa 833.3384.

Anal. Calcd for C$_{39}$H$_{63}$N$_2$O$_9$BrSi: C, 57.69; H, 7.82. Found: C, 58.03; H, 7.87.

To a solution of the bromide (32.4 mg, 0.040 mmol) in DMSO (1 mL) was added sodium azide (13 mg, 0.200 mmol). The mixture was stirred at room temperature for 16 h and was then diluted with Et$_2$O (30 mL). The resulting mixture was then washed with water and brine (30 mL each). The organic phase was next dried over anhydrous MgSO$_4$ and purified by flash chromatography using ethyl acetate−hexanes (1:4) as eluant to afford (+)-**17** (24.7 mg, 80% yield) as a light yellow oil: $[\alpha]_D^{23}$ +117.5 (*c* 0.280, CHCl$_3$); IR (CHCl$_3$) 3520 (w), 3010 (m), 2960 (s), 2100 (m), 1705 (s), 1605 (s), 1400 (s), 1250 (s), 1225 (s), 1060 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.44 (br m, 2 H), 5.93 (br m, 2 H), 5.32 (br m, 4 H), 4.70 (br m, 4 H), 4.60 (br m, 3 H), 3.57 (m, 3 H), 3.49 (dd, *J* = 9.5, 5.4 Hz, 2 H), 3.15 (dd, *J* = 12.4, 7.3 Hz, 1 H), 2.93 (br dd, *J* = 12.2, 3.3 Hz, 1 H), 2.81 (br m, 2 H), 2.39 (dd, *J* = 13.5, 5.7 Hz, 1 H), 2.03 (br m, 1 H), 1.92 (dd, *J* = 14.3, 9.6 Hz, 1 H), 1.64 (br m, 1 H), 1.60 (br m, 1 H), 1.44 (br m, 3 H), 1.22 (br m, 2 H), 0.91 (apparent t, *J* = 8.3 Hz, 2 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.5 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.72 (d, *J* = 6.6 Hz, 3 H), 0.60 (br d, *J* = 6.6 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.83, 154.16, 149.75, 131.61, 131.35, 128.32, 124.22, 120.28, 119.29, 95.00, 71.62, 69.93, 67.76, 67.53, 66.57, 65.12, 56.49, 44.78, 42.88, 42.34, 40.40, 31.73, 25.13, 24.32, 23.81, 23.63, 23.21, 22.04, 18.12, −1.41; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) *m/z* 774.4469 [(M + H)$^+$], calcd for C$_{39}$H$_{64}$N$_5$O$_9$Si 774.4473.

Anal. Calcd for C$_{39}$H$_{63}$N$_5$O$_9$Si: C, 60.52; H, 8.20. Found: C, 60.63; H, 8.21.

Carbamate (+)-18. To a solution of (+)-**17** (6.2890 g, 8.12 mmol) in THF (81 mL) was added water (730 mg, 40.6 mmol) and triphenylphosphine (3.20 g, 12.2 mmol). The solution was heated to 40 °C and stirred for 16 h. The solution was cooled to room temperature, solid NaHCO$_3$ (1.4 g, 13.2 mmol) was added followed by FmocOSu (3.6 g, 10.7 mmol), and the resulting heterogeneous mixture was stirred for 90 min. The mixture was then diluted with EtOAc (400 mL) and washed with 10% aqueous NaHSO$_4$, 10% aqueous NaHCO$_3$, and brine (250 mL each). The organic phase was next dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using ethyl acetate−hexanes (1:3) as eluant to give (+)-**18** (5.1564 g, 65% yield) as a light yellow oil: $[\alpha]_D^{23}$ +83.3° (*c* 0.940, CHCl$_3$); IR (CHCl$_3$) 3520 (w), 3445 (w), 3005 (w), 2955 (m), 1710 (s), 1610 (m), 1400 (s), 1250 (s), 1230 (s), 1210 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.44 (br m, 2 H), 7.74 (d, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.3 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 5.93 (br m, 2 H), 5.32 (br m, 4 H), 5.11 (br s, 1 H), 4.68 (br m, 4 H), 4.60 (br m, 3 H), 4.34 (br d, *J* = 6.4 Hz, 2 H), 4.18 (br m, 1 H), 3.54 (br m, 5 H), 3.40 (br s, 1 H), 3.18 (br s, 1 H), 2.96 (br m, 1 H), 2.80 (br m, 1 H), 2.37 (dd, *J* = 13.5, 5.6 Hz, 1 H), 2.05 (br m, 1 H), 1.91 (br m, 1 H), 1.65 (br m, 2 H), 1.56 (br m, 1 H), 1.43 (br m, 2 H), 1.21 (br m, 1 H), 0.91 (apparent t, *J* = 8.4 Hz, 2 H), 0.87 (d *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H), 0.71 (d, *J* = 6.6, 3 H), 0.59 (br d, *J* = 6.5, 3 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.67, 156.50, 154.24, 149.76, 143.97, 141.28, 131.61, 127.64, 127.03, 125.08, 124.12, 119.94, 119.21, 94.98, 71.87, 69.85, 67.96, 67.47, 66.75, 65.33, 65.12, 47.23, 46.86, 42.75, 40.36, 31.71, 25.16, 24.23, 23.81, 23.69, 23.25, 23.16, 22.06, 18.10, −1.42; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) *m/z* 992.5021 [(M + Na)$^+$], calcd for C$_{54}$H$_{75}$O$_{11}$N$_3$SiNa 992.5068.

Keto-Acid (+)-19. A solution of (+)-**18** (85.9 mg, 0.089 mmol) and *p*-TsOH (84 mg, 0.442 mmol) in a 2:1 mixture of MeOH and THF (4.5 mL) was heated to 60 °C and stirred for 2 h. The solution was then concentrated in vacuo and purified by flash chromatography using ethyl acetate−hexanes (1:1) as eluant to yield the alcohol (73.3 mg, 99% yield) as a white foam: $[\alpha]_D^{23}$ +3.1 (*c* 1.245, CHCl$_3$); IR (CHCl$_3$) 3510 (w), 3450 (w), 3005 (w), 2960 (m), 1720 (s), 1700 (s), 1610 (m), 1400 (s), 1225 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.43 (br m, 2 H), 7.73 (d, *J* = 7.5 Hz, 2 H), 7.55 (d, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 5.90 (br m, 2 H), 5.29 (br m, 4 H), 5.02 (br s, 1 H), 4.63 (br m, 4 H), 4.35 (d, *J* = 6.9 Hz, 2 H), 4.18

(br t, $J = 6.6$ Hz, 1 H), 3.77 (br m, 1 H), 3.52 (br m, 1 H), 3.37 (br m, 1 H), 3.18 (br m, 1 H), 2.94 (br m, 1 H), 2.63 (br m, 1 H), 2.45 (dd, $J = 13.5, 5.8$ Hz, 1 H), 2.30 (br m, 2 H), 2.04 (br m, 2 H), 1.89 (br m, 1 H), 1.68 (br m, 2 H), 1.48 (br m, 2 H), 1.23 (br m, 2 H), 0.86 (br m, 12 H), 0.74 (d, $J = 6.7$ Hz, 3 H), 0.66 (br dd, $J = 6.6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 201.41, 200.31, 156.58, 155.62, 149.12, 143.88, 141.27, 131.56, 127.66, 127.02, 124.99, 122.34, 120.48, 119.95, 119.34, 71.99, 67.90, 67.69, 67.31, 66.77, 66.22, 64.08, 47.19, 46.82, 44.98, 43.12, 41.59, 41.01, 38.35, 37.26, 25.77, 24.54, 24.07, 23.66, 23.53, 23.22, 23.12, 21.87; high-resolution mass spectrum (FAB, thiophenol) m/z 862.4243 [(M + Na)$^+$], calcd for C$_{48}$H$_{61}$N$_3$O$_{10}$Na 862.4255.

Anal. Calcd for C$_{48}$H$_{61}$N$_3$O$_{10}$: C, 68.63; H, 7.32. Found: C, 68.72; H, 7.58.

To a solution of the alcohol (83.2 mg, 0.099 mmol) in CH$_2$Cl$_2$ (1 mL) was added Dess−Martin periodinane (168.3 mg, 0.397 mmol). The heterogeneous mixture was stirred under air for 2 h and was then concentrated in vacuo.

To a solution of the crude residue in THF (1 mL) was added 1 M Jones reagent in water (400 μL, 0.400 mmol). The mixture was stirred for 10 min and was then quenched by addition of EtOH (5 mL). The resulting mixture was diluted with EtOAc (50 mL) and washed with 10% aqueous NaHSO$_4$, 10% aqueous Na$_2$S$_2$O$_3$, and brine (50 mL each). The organic phase was next dried over anhydrous MgSO$_4$, concentrated in vacuo, and purified by flash chromatography using methanol−acetic acid−methylene chloride (2:1:97) as eluant to give (+)-**19** (67.4 mg, 78% yield for two steps) as a light yellow oil after azeotropic removal of acetic acid with benzene (2 × 10 mL): $[\alpha]_D^{23}$ +72.3° (*c* 3.055, CHCl$_3$); IR (CHCl$_3$) 3420 (w), 3010 (m), 2960 (m), 1725 (s), 1605 (m), 1510 (m), 1395 (s), 1205 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.44 (br m, 2 H), 7.73 (d, $J = 7.5$ Hz, 2 H), 7.55 (br m, 2 H), 7.36 (t, $J = 7.4$ Hz, 2 H), 7.27 (br m, 2 H), 5.91 (br m, 2 H), 5.58 (br s, 1 H), 5.30 (br m, 4 H), 4.67 (br m, 4 H), 4.33 (br m, 2 H), 4.18 (t, $J = 7.0$ Hz, 1 H), 3.99 (br m, 1 H), 3.71 (br m, 1 H), 3.54 (br m, 1 H), 2.79 (br m, 1 H), 2.40 (br m, 1 H), 2.03 (br m, 2 H), 1.78 (br m, 1 H), 1.57 (br m, 3 H), 1.41 (br m, 2 H), 1.26 (br m, 2 H), 0.91 (d, $J = 6.1$ Hz, 3 H), 0.85 (br m, 6 H), 0.75 (br m, 6 H), 0.63 (br m, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.58, 199.04, 198.61, 177.88, 156.10, 155.32, 148.53, 143.90, 143.73, 141.24, 131.53, 131.34, 127.65, 127.01, 125.02, 119.92, 119.60, 119.40, 119.11, 118.84, 70.42, 69.55, 68.06, 67.53, 67.12, 51.81, 47.06, 45.64, 44.63, 42.52, 41.33, 40.74, 37.70, 37.37, 29.64, 25.69, 24.53, 24.04, 23.78, 23.45, 23.21, 22.36, 22.11; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) m/z 874.3876 [(M + Na)$^+$], calcd for C$_{48}$H$_{57}$N$_3$O$_{11}$Na 874.3891.

Bispyrrolinone (−)-5. To a solution of (+)-**19** (890.7 mg, 1.03 mmol) in CH$_2$Cl$_2$ (10.5 mL) were added acetic acid (155 mg, 2.58 mmol) and (Ph$_3$P)$_2$PdCl$_2$ (14.5 mg, 0.021 mmol). Tributyltin hydride (830 μL, 2.64 mmol) was then added quickly and in one portion via syringe; vigorous gas evolution was observed along with a darkening of the color of the solution. The solution was stirred for 5 min, concentrated in vacuo, and purified by flash chromatography using methanol−acetic acid−methylene chloride (7:2:191) as eluant to afford

(−)-**5** (505.2 mg, 72% yield) as a light tan foam after azeotropic removal of acetic acid with benzene (5 × 50 mL): $[\alpha]_D^{23}$ −123.2° (*c* 0.945, CHCl$_3$); IR (CHCl$_3$) 3670 (w), 3440 (m), 3005 (m), 2960 (s), 1715 (s), 1660 (m), 1570 (m), 1510 (m), 1445 (m), 1210 (m), 1165 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.22 (d, $J = 3.7$ Hz, 1 H), 7.89 (d, $J = 3.8$ Hz, 1 H), 7.73 (d, $J = 7.6$ Hz, 2 H), 7.67 (br s, 1 H), 7.56 (d, $J = 7.2$ Hz, 2 H), 7.37 (t, $J = 7.4$ Hz, 2 H), 7.28 (t, $J = 7.4$ Hz, 2 H), 7.01 (br s, 1 H), 5.53 (br s, 1 H), 4.36 (d, $J = 7.0$ Hz, 2 H), 4.19 (t, $J = 7.0$ Hz, 1 H), 4.06 (dd, $J = 19.8, 4.9$ Hz, 1 H), 3.99 (dd, $J = 19.4, 4.6$ Hz, 1 H), 3.42 (m, 1 H), 2.86 (d, $J = 16.7$ Hz, 1 H), 2.43 (d, $J = 16.6$ Hz, 1 H), 1.93 (dd, $J = 14.1, 4.7$ Hz, 1 H), 1.78 (m, 1 H), 1.66 (m, 2 H), 1.53 (m, 4 H), 1.31 (m, 1 H), 0.89 (d, $J = 6.5$ Hz, 3 H), 0.87 (d, $J = 6.5$ Hz, 3 H), 0.85 (d, $J = 6.7$ Hz, 3 H), 0.81 (d, $J = 6.6$ Hz, 3 H), 0.73 (d, $J = 6.5$ Hz, 3 H), 0.60 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.57, 202.93, 201.90, 176.03, 163.11, 161.31, 156.29, 143.67, 141.27, 127.75, 127.06, 125.00, 119.99, 108.42, 68.66, 68.41, 67.27, 51.42, 47.05, 46.48, 45.66, 43.55, 40.43, 25.73, 24.57, 24.42, 24.16, 24.07, 23.76, 23.41, 22.46, 21.99; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) m/z 706.3452 [(M + Na)$^+$], calcd for C$_{40}$H$_{49}$N$_3$O$_7$Na 706.3468.

Anal. Calcd for C$_{40}$H$_{49}$N$_3$O$_7$: C, 70.26; H, 7.22; N, 6.14. Found: C, 70.04; H, 7.60; N, 5.78.

Pyrrolinone−Peptide Hybrid Ligand 3. Fmoc-Thr(*t*-Bu)-Wang resin (95 mg, 0.05 mmol) was subjected to solid-phase synthesis using five coupling cycles to sequentially add Fmoc-Ala, Fmoc-Leu, Fmoc-Lys(Boc), Fmoc-Leu, and Fmoc-Thr(*t*-Bu). The resin was deprotected and then coupled to (−)-**5** (51 mg, 0.075 mmol) by treatment with HBTU (28 mg, 0.074 mmol) and diisopropylethylamine (39 μL, 0.224 mmol) for 18 h. An additional three coupling cycles were then performed to incorporate Fmoc-Tyr(*t*-Bu), Fmoc-Lys(Boc), and Fmoc-Pro. Removal of the N-terminal Fmoc group, vacuum-drying of the resin, treatment with trifluoroacetic acid, and preparative HPLC purification of the crude hybrid ligand yielded 12.9 mg of the hybrid ligand **3** as a white, amorphous powder of >98% purity by HPLC: AAA Thr 2.20 (2); Pro 0.99 (1); Ala 1.06 (1); Leu 2.04 (2); Tyr 0.93 (1); Lys 1.90 (2); mass spectrum (FAB) m/z 1477.9 [(M + H)$^+$], calcd for C$_{74}$H$_{120}$N$_{14}$O$_{17}$ 1477.84.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for **20**, **22**−**24**, **27**−**31** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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