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Molecular Modeling, Synthesis, and Structures of *N*-Methylated 3,5-Linked Pyrrolin-4-ones Toward the Creation of a Privileged Nonpeptide Scaffold

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Abstract—The molecular modeling, synthesis, and elucidations of the solid state and solution structures of *N*-methylated 3,5-linked bispyrrolin-4-ones are described. Prior investigations established that the 3,5-linked pyrrolin-4-one based scaffold can be incorporated into mimics of β-sheet/β-strands and into potent, orally bioavailable inhibitors of the HIV-1 protease. To extend the utility of this scaffold beyond that of the initially designed mimics of β-sheet/β-strands, we have now explored the structure of *N*-methylated pyrrolinones. Molecular modeling indicated that *N*-methylated bispyrrolinones could adopt three low-energy backbone conformations (ca. 165°, 289°, and 320°). Upon their successful synthesis, structural elucidation both in the solid state and in solution revealed the existence of two of the three predicted backbone conformers (ca. 165° and 289°). Two structures were particularly noteworthy and completely unexpected. Mono-*N*-methyl bispyrrolinone (+)-**1** self assembled in the solid state to form a novel helix, while the acetylene-linked dimer of (+)-**1**, designed to potentiate the observed helical array, instead associated via an intermolecular hydrogen bond in parallel columns. These serendipitous observations led us to speculate that the pyrrolinone moiety may in fact represent a privileged nonpeptide scaffold, able to mimic not only the extended β-sheet/β-strand conformation as initially targeted, but also diverse conformations including those analogous to β-turns and helices. These seemingly unlimited conformations greatly expand the scope of this scaffold for the development of low-molecular weight ligands for biologically important macromolecules.

Introduction

Peptides and proteins primarily adopt three regularly folded secondary structural motifs: β-sheets, β-turns, and helices.[1] With just one repeating unit (the peptide bond), these biopolymers generate tertiary structures that have myriad shapes and biological functions. The design and synthesis of a privileged nonpeptide scaffold, which could adopt the three principle conformations of peptides and proteins, but which would be devoid of the known associated poor pharmokinetic properties, would constitute a significant advance in molecular mimicry. To date, most known scaffolds can adopt only one conformation.[2] Ideally, conformational control of a privileged nonpeptide scaffold would be effected via simple structural modification of the individual monomers. Such a scaffold would hold considerable promise for the development of low-molecular-weight nonpeptide ligands for biologically important macromolecules.

Our investigations of the *N*-unsubstituted 3,5-linked polypyrrolin-4-one scaffold have already furnished biologically potent mimetics of β-sheets (Fig. 1).[3] These peptidomimetics, which are stable to proteases,[3h] adopt an extended conformation, both in solution[4] and in the

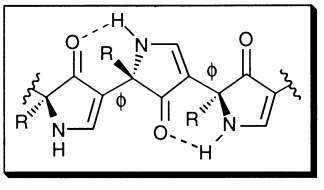

Figure 1. 3,5-linked polypyrrolin-4-ones.

solid state,[3a,d] which is stabilized by intramolecular H-bonds between adjacent rings with dihedral angles between the rings (ϕ angles) of ca. 205° (Figure 2, Panel a).[3a,d] We have proposed that the intramolecular H-bonds may account, at least in part, for the improved membrane transport of pyrrolinone-based HIV-1 protease inhibitors, compared with their peptidal counterparts, due to a decreased energy penalty for desolvation.[3f] Importantly, the pyrrolinone based inhibitors bind to the enzyme in a manner generally resembling that of more conventional inhibitors, but with

Key words: Peptides and polypeptides; mimetics; molecular modeling/mechanics; X-ray crystal structures.

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features that are *sui generis*.[3h] Thus, the 3,5-linked polypyrrolin-4-one scaffold displays several unique features.

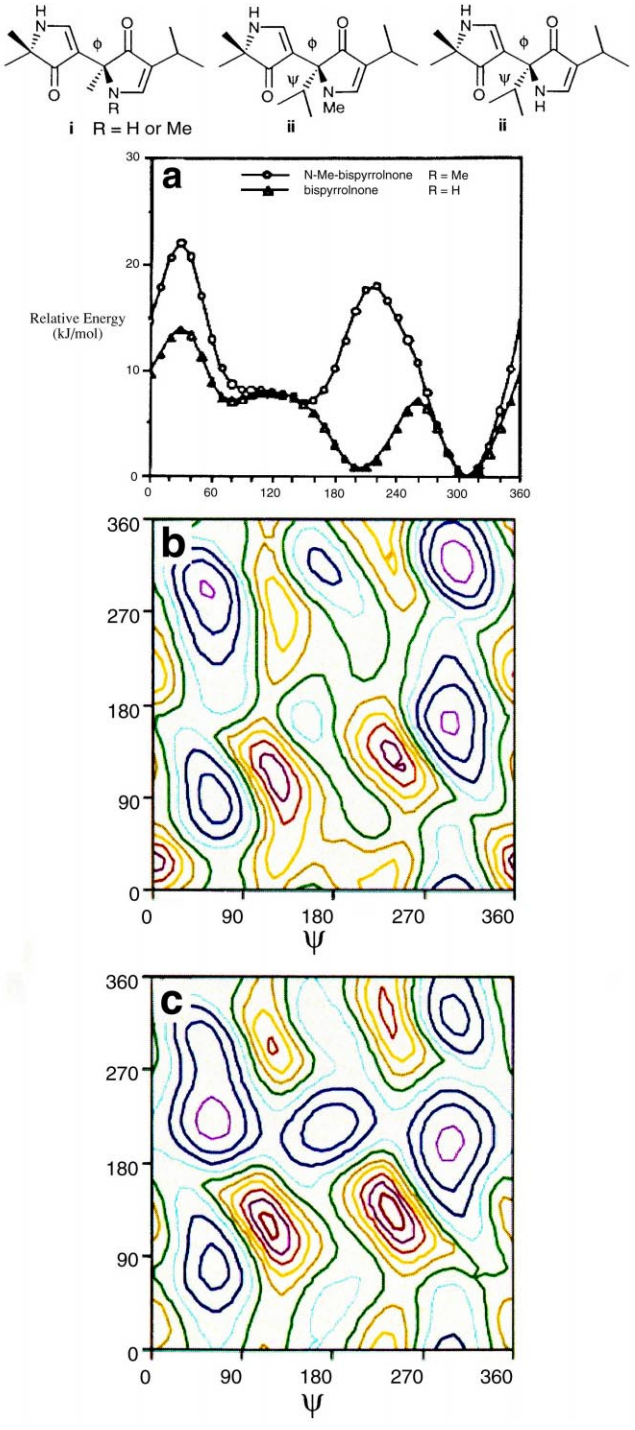
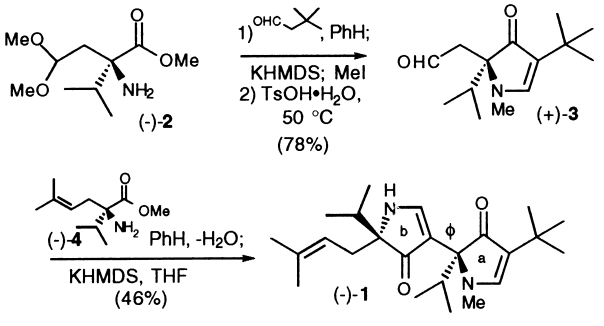


Figure 2. Panel a represents relative energy versus ϕ of model bis-3,5-linked pyrrolin-4-ones **i**. Panels b and c represent energy contour plots of model bis-3,5-coupled-pyrrolinones **ii** and **iii** as a function of the ϕ versus ψ angles. Colour indicates the varying energy levels with highest to lowest energy level represented as red, orange, yellow, olive, green,

Recently, two serendipitous observations in our laboratory (vide infra) have led us to speculate that the 3,5-linked polypyrrolin-4-one scaffold may in fact provide access not only to the extended β-sheet/β-strand conformation as initially targeted,[3] but also to other diverse conformations including those analogous to β-turns and helices. Molecular mechanics calculations with the MM2 force field indicated that the low-energy conformation of a *N*-methylated bispyrrolinone with methyl groups as side chains would contain a dihedral angle (ϕ) of 310°, corresponding to a turned conformation (Figure 2, Panel a).[5] The use of only methyl groups for the side-chain substituents, however, proved to be an oversimplification since further calculations revealed that β-branching of the side chains does significantly affect the predicted energy of rotation about the ϕ bond, leading to three minima at ca. 165°, 289°, and 320° (Figure 2, Panel b). Similar calculations on *N*-unmethylated pyrrolinones with β-branched side chains generated only one low-energy conformer (ϕ = ca. 205°) corresponding to the observed extended strand conformation (Figure 2, Panel c). In this paper, we report our investigations on the conformational effects of *N*-methylation of the 3,5-linked polypyrrolin-4-one scaffold.

Based on the above modeling, we selected *N*-methylated bispyrrolinone **1** as our initial target. Aldehyde (+)-**3** was assembled via our now well-established methodology for the synthesis of 3,5,5-trisubstituted pyrrolin-4-ones (Scheme 1).[3a,b,d] The sequence began with condensation of known amine (−)-**2**[4,6] with 3,3-dimethyl-



Scheme 1.

butyraldehyde. The aldehyde moiety in (−)-**2** was masked as a dimethyl acetal rather than an olefin, in recognition of the enhanced susceptibility of *N*-methylated pyrrolinones toward oxidative cleavage. After cyclization with KHMDS and quenching with methyl iodide, acetal hydrolysis and a second pyrrolinone construction using known amine (−)-**4**[3d] afforded bispyrrolinone (−)-**1**. The X-ray crystal structure of (−)-**1**[7] showed a ϕ angle of 177.1° (Fig. 3). In view of the molecular modeling results, the small ϕ-angle deviation from the extended conformation (ca. 205°) was not unexpected as this is close to one of the three predicted low energy conformations (ϕ = 165°) (Figure 2, Panel b).

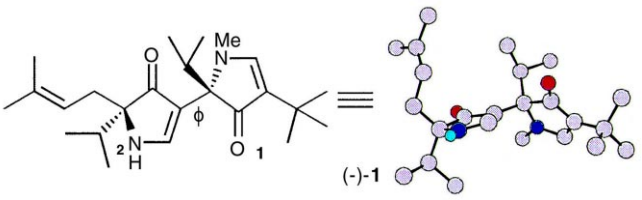


Figure 3. X-Ray structure of bispyrrolinone (−)-**1**.[7] Oxygens and nitrogens are depicted in red and blue respectively.

Even more intriguing is the intermolecular hydrogen bond from O(1) of one molecule to the hydrogen on N(2) of a second molecule in the unit cell of bispyrrolinone (−)-**1** (Fig. 4), resulting in an extended helical array in the solid state. This observation suggested that the *N*-methylated pyrrolinone structural motif, containing neither α-amino acids nor nucleic acids,[1,8] might afford novel helices in the solid state and in solution.

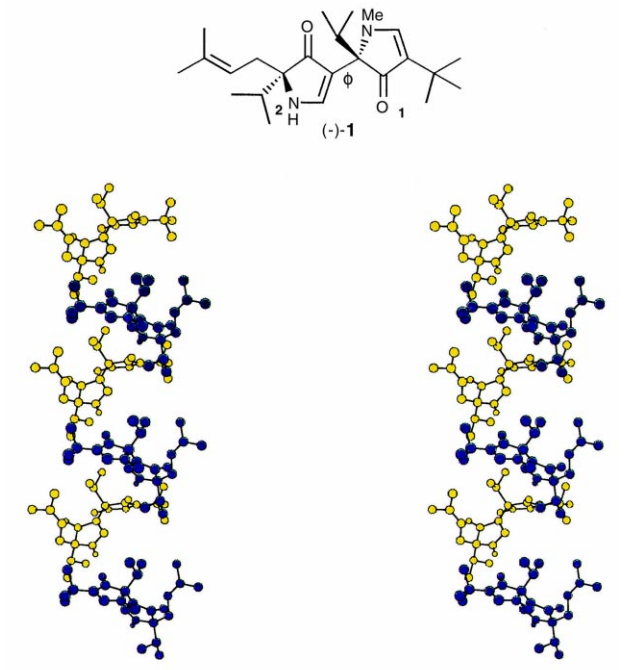
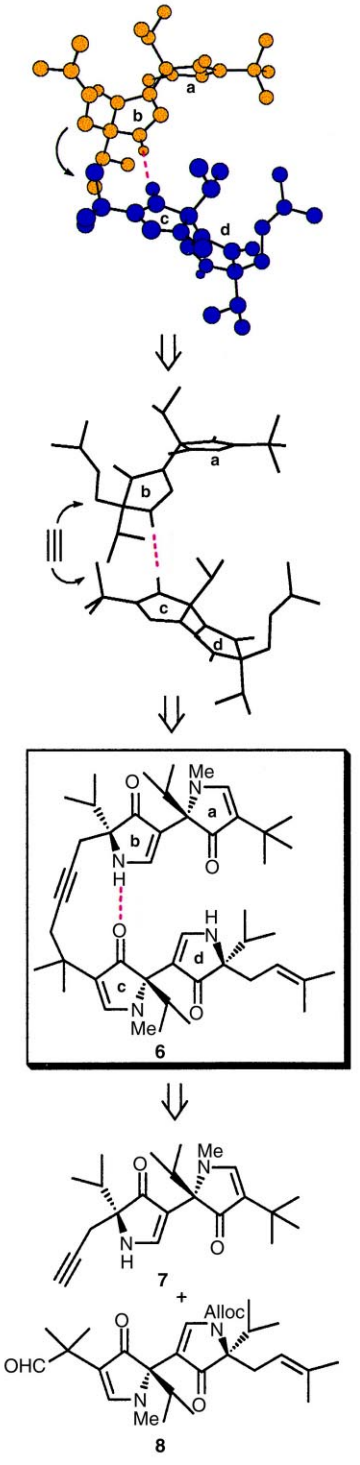


Figure 4. Stereo views of X-Ray structure of bispyrrolinone (−)-**1**.[7] Molecules in the foreground are blue while those in the background are maize.

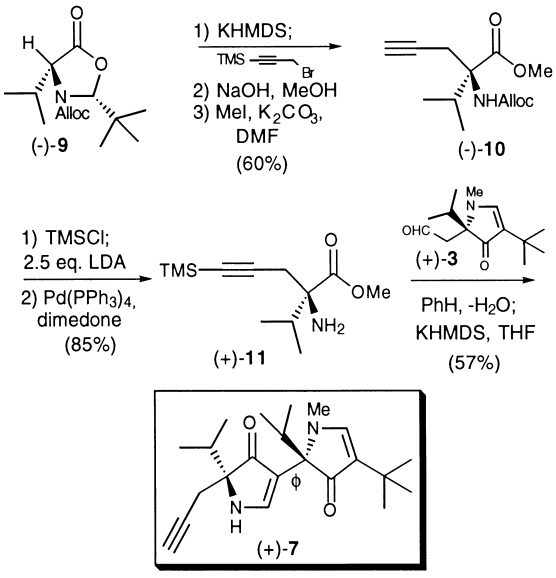
To design a helix based on the 3,5-linked pyrrolinone scaffold, we envisioned that a covalent linker joining the prenyl group of one bispyrrolinone to the *tert*-butyl moiety of an adjacent bispyrrolinone (Scheme 2) would serve to enforce the helical conformation evident in the crystal structure of (−)-**1**. Molecular modeling (MM2) predicted that an alkynyl linker might prove ideal, providing sufficient rotational flexibility to accommodate the O(1) to N(2) intramolecular H-bond, while affording sufficient rigidity to overcome unfavorable entropic factors. Towards this end, we designed tetrapyrrolinone **6** (Scheme 2) which we anticipated would constitute one turn of a pyrrolinone-based helix.



Scheme 2.

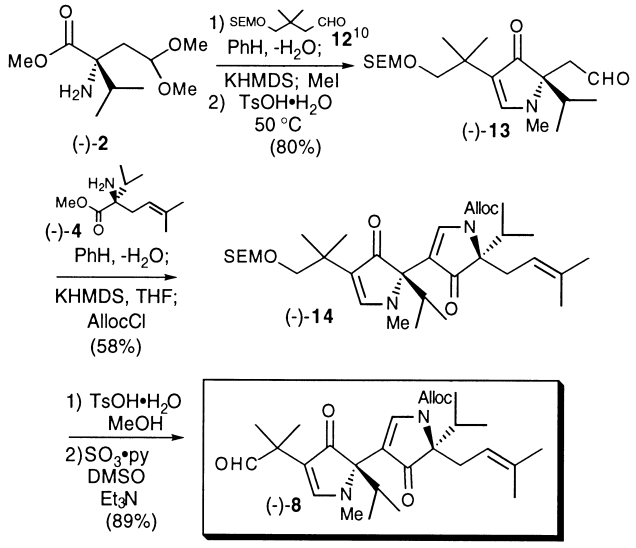
From the retrosynthetic perspective, tetrapyrrolinone **6** would derive from the coupling bispyrrolinone **7** with **8** (Scheme 2). Bispyrrolinone **7** was assembled in a manner analogous to (−)-**1**. Alkynylation of oxazolidinone (−)-**9**[3d] with trimethylsilyl propargyl bromide (Scheme 3),[9] followed by hydrolysis and esterification furnished alkynyl ester (−)-**10** in 60% yield (three steps). Resilylation of the alkyne and removal of the Alloc unit then afforded amino ester (+)-**11** in 85% yield. Condensa-

tion of the latter with monopyrrolinone (+)-**3** and cyclization with concomitant TMS removal furnished the requisite bispyrrolinone (+)-**7** in 57% yield (mp 89–92 °C); utilization of the nonsilylated alkyne of (+)-**11** resulted in a low yield of (+)-**7**.



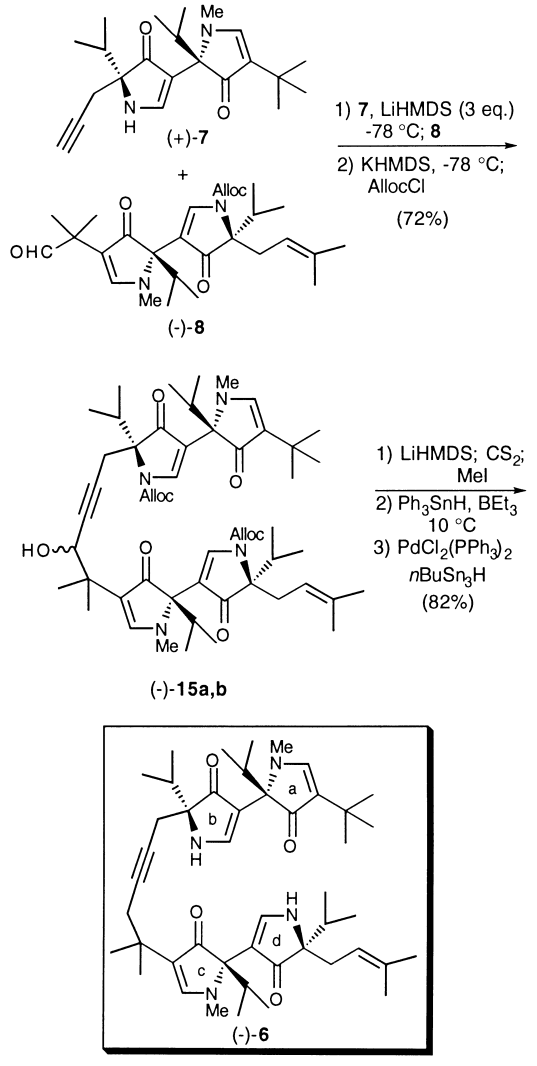
Scheme 3.

Synthesis of coupling partner (−)-**8** (Scheme 4) began with (−)-**2** and entailed two iterations of our pyrrolinone synthetic protocol to furnish (−)-**14**.[10] Hydrolysis of the 2-(trimethylsilyl) ethoxymethyl (SEM) ether and Parikh–Doering[11] oxidation then furnished aldehyde (−)-**8**; the overall yield from (−)-**2** was 41% for the five-step sequence.



Scheme 4.

Optimal conditions for the union of (+)-**7** and (−)-**8** entailed formation of the dianion of (+)-**7** followed by addition of aldehyde (−)-**8** at low temperature (Scheme 5). Protection as the *N*-allyl carbamates afforded the separable tetrapyrrolinones (−)-**15a** and (−)-**15b** in 72% yield. Individually (−)-**15a** and (−)-**15b** were deoxygenated via the Barton protocol[12] with Et_3B as the radical initiator.[13] Palladium-catalyzed removal of the Alloc group[14] then completed the synthesis of tetrapyrrolinone (−)-**6** (mp 211–212 °C; 59% yield, three steps).



Scheme 5.

While the synthesis of (−)-**6** was underway, we performed an X-ray analysis of crystalline bispyrrolinone (+)-**7**[15] (Fig. 5), an analogue of (−)-**1** containing a

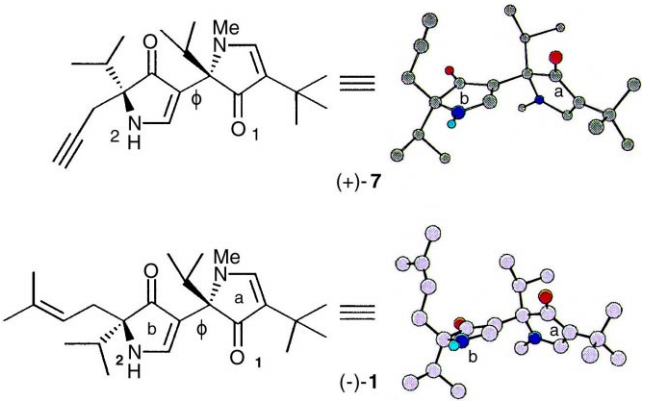


Figure 5. X-ray structure of bispyrrolinones (+)-**7** and (−)-**1**.[15]

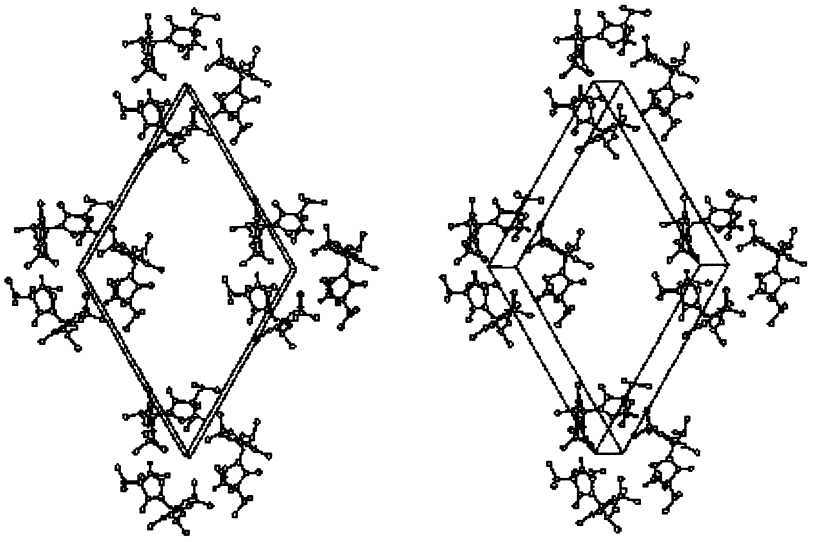


Figure 6. Crystal packing of bispyrrolinone (+)-**7**.[15]

terminal alkyne in place of the trisubstituted olefin. The ϕ dihedral angle in (+)-**7** proved to be 169.8°, similar to the corresponding value for (−)-**1** (177.1°). However, in contrast with the helical arrangement of the bispyrrolinone observed in the crystal structure of (−)-**1**, (+)-**7** associated in the crystal lattice as a ring of three molecules (Fig. 6), with a threefold axis of symmetry, and an intermolecular H-bond between the O(1) of ring **a** and N(2) of ring **b**. The smaller steric demand of the alkynyl substituent in (+)-**7** does not appear to favor the helical conformation as observed in (−)-**1** (Fig. 4). Instead, the alkynyl substituent of (+)-**7** is orientated on the same side of the three molecule ring present in crystal packing (Fig. 6). In (−)-**1** the alkene substituent appears to preclude formation of a similar three molecule ring due to the steric bulk of the trisubstituted olefin. In fact, the steric bulk may well be important in stabilizing the helical crystal packing by filling space in the helical groove.

With the synthesis of (−)-**6** complete, the X-ray crystal structure (Fig. 7)[16] revealed an intramolecular H-bond between NH(2) and O(4), not between NH(2) and O(3) as we had predicted. Interestingly, the ϕ dihedral angle between pyrrolinones **a** and **b** in (−)-**6** (Fig. 7) is 168.3°, similar to the observed values in both (−)-**1** and (+)-**7**, whereas the orientation of pyrrolinones **c** and **d** (ϕ = 289.4°) more closely resembled one of the other low-energy conformers with ϕ = 289° (Figure 2, Panel b). In the crystal lattice, (−)-**6** aligns in a column with an intermolecular H-bond between the carbonyl O(2) of ring **b** of one tetrapyrrolinone and the N(4) of ring **d** in a second tetrapyrrolinone (Fig. 8).

With the solid state structural information on tetrapyrrolinone (−)-**6** secure, we next turned to an analysis of the solution conformation. Tetrapyrrolinone (−)-**6** was designed to form a hydrogen bond between the N-H in pyrrolinone ring **b** and the carbonyl of ring **c** (see Scheme 2). To determine if in fact such a hydrogen bond exists in solution we examined the solution IR and NMR. The FT-IR spectrum of (−)-**6**, taken in a non-hydrogen bonding solvent (CH_2Cl_2) under concentration conditions such that intermolecular hydrogen

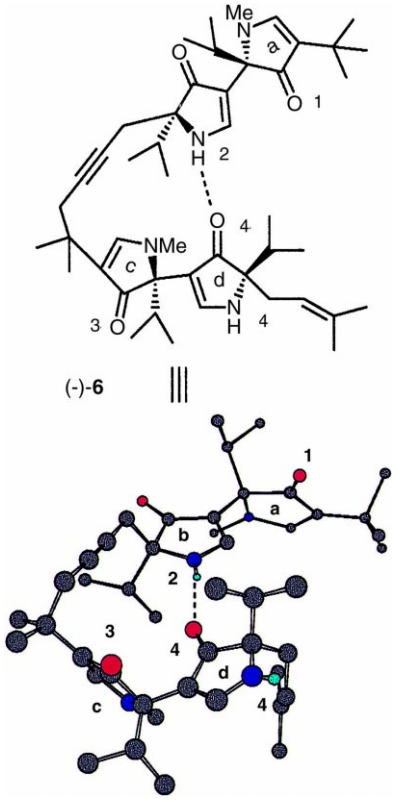


Figure 7. X-ray structure of tetrapyrrolinone (−)-**6**.[16]

bonding would not be expected (e.g. 0.001 M), displayed a sharp absorption at 3441 cm^{-1}, indicative of a non-hydrogen bonded pyrrolinone N-H (Fig. 9).[4] Also observed was a broad absorption at 3260 cm^{-1} indicative of an intramolecular pyrrolinone N-H hydrogen bond.[4] The nature and extent of intramolecular hydro-

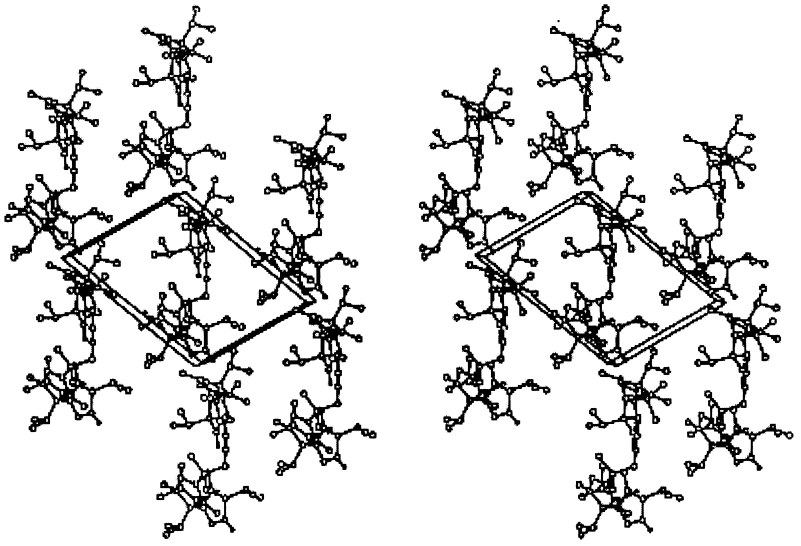


Figure 8. Crystal packing of tetrapyrrolinone (−)-**6**.[16]

gen bonding of the pyrrolinone N-Hs was next examined via the temperature dependence of the ^{1}H NMR chemical shifts.[17]

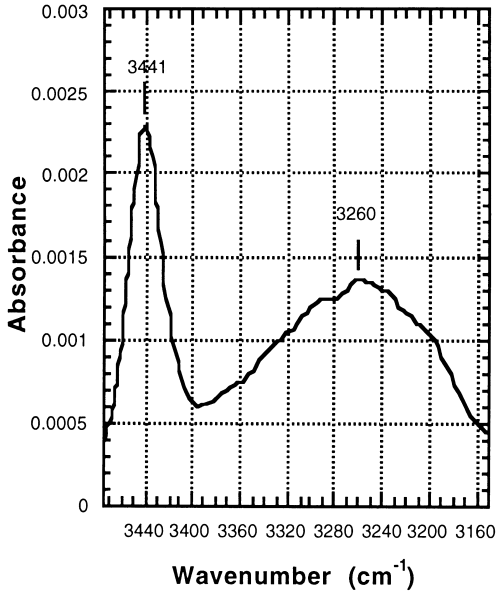


Figure 9. FT-IR of tetrapyrrolinone (−)-**6** in CH_2Cl_2 at 0.001 M.

The chemical shift dependence of (−)-**6** was determined in three nonparticipating solvent systems (CD_2Cl_2, $CDCl_3$ and 9:1 CCl_4:C_6D_6). All experiments were carried out at concentrations below the critical value for self-association for the entire temperature range of the experiments.[18,19] Nonhydrogen bonded pyrrolinone N-H chemical shifts are generally observed at 5–5.5 ppm, whereas strongly hydrogen bonded N-H chemical shifts are observed at 7.5–8 ppm.[4] Amide hydrogens, which participate in strong hydrogen bonds or are not hydrogen bonded, display small temperature dependent chemical shifts (ca. −2 to −4 ppb/K).[19] Peptide amide hydrogens involved in dynamic hydrogen bonds produce much larger temperature effects.[20] It would seem reasonable to assume that pyrrolinones will have similar hydrogen bonding profiles to that of peptides considering their close structural homology (amide versus vinylogous amide). In (−)-**6** both of the N-H hydrogens displayed temperature effects indicative of hydrogens engaged in dynamic hydrogen bonds (Fig. 10). The upfield N-H was assigned to pyrrolinone ring **d** by observation of an NOE cross peak with the vinyl proton of the trisubstituted olefin and also by the spin coupling of this N-H to the proton furthest downfield, corresponding to the vinyl proton of ring **d**. This assignment was made by long range proton carbon coupling. The downfield N-H was, therefore, assigned by elimination to pyrrolinone ring **b**. The downfield N-

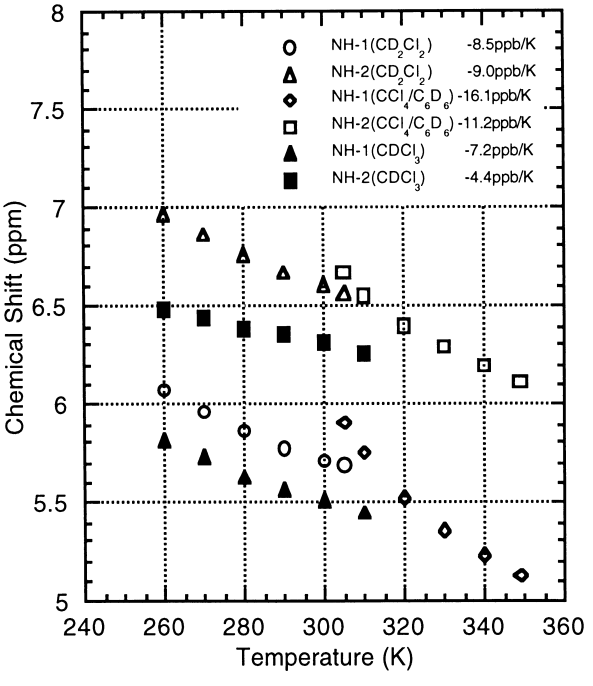


Figure 10. VT-NMR of tetrapyrrolinone (−)-**6**.

H of (−)-**6** displayed a chemical shift dependence of −4.4 ppb/K. That the observed downfield N-H (on ring **b**) is involved in a dynamic hydrogen bond due to its proximity to the carbonyl oxygens of pyrrolinone rings **c** and **d** was not surprising [cf. the desired (i.e. designed) hydrogen bond was between the N-H of pyrrolinone ring **b** and the carbonyl of ring **c**, while that observed in the X-ray structure was between the N-H in ring **b** and the carbonyl of ring **d**]. The upfield N-H also displayed large temperature shift dependence; the latter observation was unexpected due to what was thought to be its inability to participate in an intramolecular hydrogen bond. Only in $CDCl_3$ did any of the N-H hydrogens display a chemical shift dependence close to that observed for a N-H involved in a strong hydrogen bond (−2 to −4 ppb/K).

In an attempt to refine further the solution conformation, we performed 2-D NMR experiments. The nature of the isolated spin systems in (−)-**6** precluded the use of coupling constants to define the solution conformation, as is possible with polypeptides. Instead, the most conclusive indication of a defined conformation for (−)-**6** would arise via the observance of NOEs from hydrogens on pyrrolinone rings **a** and **b** with hydrogens on rings **c** and **d**. Unfortunately, in conformations in which a hydrogen bond exists between the N-H on ring **b** and the carbonyl oxygens of either rings **c** or **d**, most of the hydrogens are too far removed to display NOE interactions to the hydrogens on pyrrolinone rings **a** or **b**.

Not withstanding these geometrical constraints, a NOESY experiment (600 MHz; mix time of 750 ms)[21] was conducted. The solvent of choice appeared to be $CDCl_3$ since the VT-NMR studies suggested that this solvent lead to the strongest intramolecular hydrogen bond of the downfield N-H. A significant NOE was observed between the vinyl C-H of pyrrolinone **d** and the methine hydrogen of the isopropyl side chain on pyrrolinone ring **c** (Fig. 11). Employing the observed NOE between the propargylic methylene hydrogens in (−)-**6** as an internal standard,[22] the calculated distance between the vinyl C-H of pyrrolinone **d** and the methine proton of the isopropyl side chain of pyrrolinone ring **c** was 2.24 Å. Importantly, the distance between the same two hydrogens in the X-ray structure was 2.22 Å. This distance is possible only if the dihedral angle between rings **c** and **d** is ∼285°, the angle observed in the crystal structure of (−)-**6** (Fig. 7). If in solution the dihedral angle between pyrrolinone rings **a** and **b** is identical with that observed in the crystal structure (ca. 168°), then an NOE would not be anticipated between the vinyl C-H on ring **b** and the methine hydrogen of the isopropyl side chain of ring **a**. Importantly, no NOE cross peak was observed. However, further inspection of the ^1H NMR spectrum of (−)-**6** suggested the possibly of a minor rotamer present in solution. In particular, a resonance at 4.78 ppm for a vinyl hydrogen is present amounting to 5% of the intensity of the vinyl hydrogen resonance of the trisubstituted olefin observed at 4.95 ppm for the major rotamer. Taken together, the IR and NMR data support a conformation in solution for (−)-**6** quite similar to that observed in the solid state. In particular a

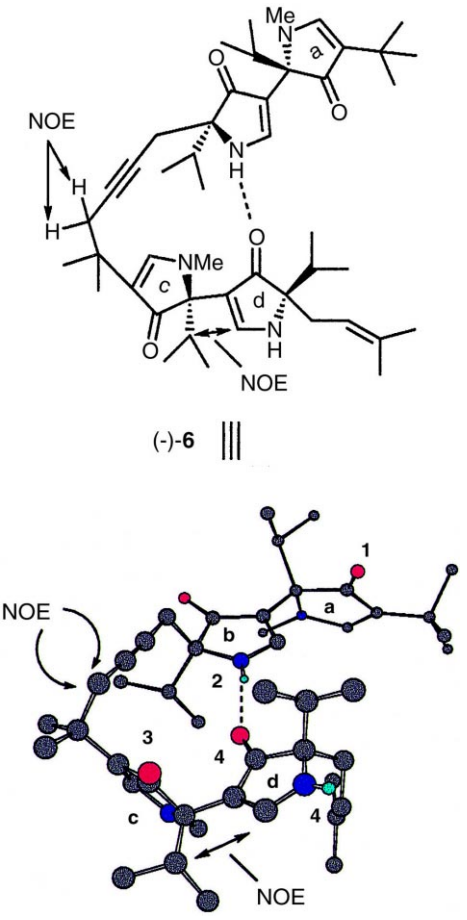


Figure 11. NOE data of and X-ray structure of tetrapyrrolinone (−)-**6**.

dynamic hydrogen bond was observed between bispyrrolinones **b** and **d**. Moreover the observed NOE cross resonance is indicative of the same dihedral angle (ϕ) between pyrrolinone rings **c** and **d** in solution as observed in the crystal structure of (−)-**6**.

In summary, our solid state and solution structural information demonstrate that diverse conformations can be accessed via simple structural perturbations of the pyrrolinone scaffold (Fig. 12). These additional conformations significantly expand the three-dimensional conformational space accessible to the 3,5-linked pyrrolin-4-one scaffold, and thereby the range of potential applications for this potentially privileged scaffold in molecular mimicry. Studies to explore related structural modifications of the 3,5-linked pyrrolin-4-one scaffold (cf. in a library mode), including the introduction of *d*- and *l*-pyrrolinone units, in conjunction with our recently introduced 2,5-linked pyrrolinone scaffold (i.e. the carbonyl displaced pyrrolinones),[24] will be reported in due course.

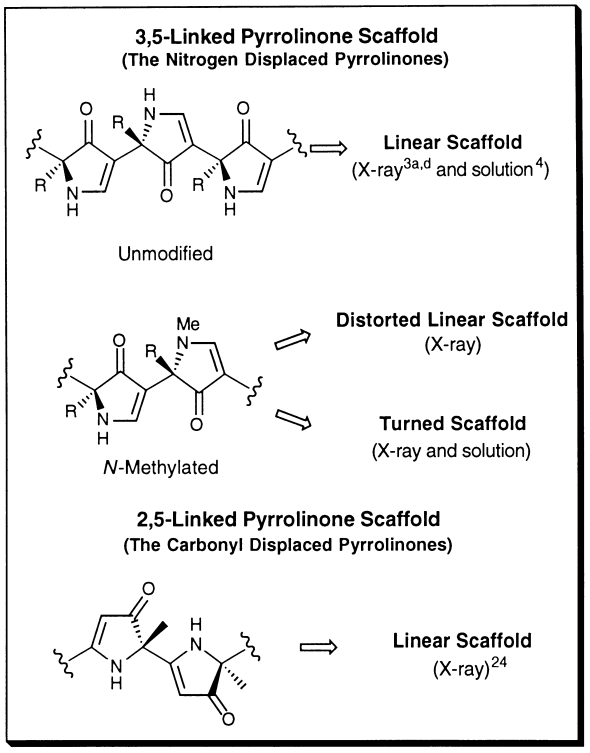


Figure 12. Diverse backbone conformations accessible via pyrrolinone scaffolds.

Experimental[25]

Monopyrrolinone (+)-3. At room temperature a solution of amino ester (−)-**2** (5.52 g, 11.5 mmol) in benzene (23 mL) was treated with 3,3-dimethyl butyraldehyde (2.16 mL, 17.2 mmol). Condensation was effected by allowing the mixture to stand for 1.5 h followed by concentration in vacuo and azeotropic dehydration with additional benzene (2×23 mL). An additional 1.44 mL of 3,3-dimethyl butyraldehyde (11.5 mmol) and benzene (23 mL) was added and the solution was allowed to stand for 1 h. Following concentration in vacuo and azeotropic dehydration with additional benzene (4×23 mL), the residue was placed under high vacuum overnight. The resultant oil was then dissolved in THF (115 mL) and 0.5 M KHMDS in toluene (80.3 mL, 40.1 mmol) was added dropwise rapidly at room temperature and the solution allowed to stir for 15 min. Iodomethane (2.14 mL, 34.4 mmol) was added and after 15 min the mixture was quenched with 10% aqueous $NaHSO_4$ (150 mL), and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ and brine (150 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (20% ethyl acetate:hexanes) gave the monopyrrolinone dimethyl acetal (2.66 g, 82% yield) as an off white foam: $[\alpha]_D^{20}$ +55.1° (c = 1.34, $CDCl_3$); IR ($CHCl_3$) 3000 (s), 2960 (s), 2830 (m), 1645 (s), 1575 (s), 1480 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 3H), 3.98 (t, J = 4.5 Hz, 1H), 3.19 (s, 3H), 3.15 (s, 3H), 2.13 (dd, J = 14.3, 4.3 Hz, 1H); 1.85 (apparent sep, J = 7.0 Hz, 1H) 1.12 (s, 9H), 0.85 (apparent sep, J = 6.8 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δd 201.3, 161.2, 120.0, 102.4, 72.5, 54.2, 52.9, 36.7, 34.6, 33.6, 29.8, 29.1, 16.8, 15.2; high resolution mass spectrum (CI, N-H_3) m/z 284.2237 [$(M+H)^+$; calcd for $C_{16}H_{29}NO_3$: 284.2225].

To a solution of the monopyrrolinone dimethyl acetal (1.02 g, 3.60 mmol) in a 3:1 mixture of THF:water (36 mL) was added TsOH (6.9 mg, 0.036 mmol). The reaction was heated at 55 °C for 1.5 h and was then diluted with ethyl acetate (100 mL) after being allowed to cool to room temperature. The mixture was washed with 50% sat. aq. $NaHCO_3$ and brine (100 mL each). The organic phase was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (20% ethyl acetate:hexanes) afforded (+)-**3** (865 mg, 95% yield) as a clear, colorless oil: $[\alpha]_D^{20}$ +39.0° (c = 0.29, $CDCl_3$); IR ($CHCl_3$) 3000 (s), 2960 (m), 1720 (s), 1650 (s), 1570 (s), 1350 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.22 (dd, J = 5.08, 0.41 Hz, 1H), 7.48 (s, 1H), 2.99 (d, J = 14.2 Hz, 1H), 2.96 (s, 3H), 2.54 (dd, J = 14.2, 5.6 Hz, 1H), 2.00 (heptet, J = 6.9 Hz, 1H), 1.16 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 199.9, 161.8, 121.3, 72.6, 47.4, 33.6, 33.4, 30.0, 29.0, 16.4, 15.1; high resolution mass spectrum (CI, CH_4) m/z 237.1721 [$(M+H)^+$; calcd for $C_{14}H_{23}NO_2$: 237.1729].

Bispyrrolinone (−)-1. At room temperature a solution of aldehyde (+)-**3** (63.1 mg, 0.266 mmol) in benzene (1.0 mL) was treated with amino ester (−)-**4** (52.7 mg, 0.266 mmol). Condensation was effected via concentration in vacuo followed by azeotropic dehydration with additional benzene (2×1.0 mL). The resultant oil was dissolved in THF (2.7 mL) and 0.5 M KHMDS in toluene (1.9 mL, 0.93 mmol) was added dropwise rapidly at room temperature. The mixture was stirred for 10 min, quenched with 10% aqueous $NaHSO_4$ (10 mL), and extracted with Et_2O (3×10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine (20 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (20% EtOAc in hexanes) gave (−)-**1** (47.5 mg, 46% yield) as a clear, colorless oil. An analytical sample was crystallized from i-Pr_2O at 0 °C to give clear, colorless prisms: mp 153 °C (softness at 138 °C); $[\alpha]_D^{20}$ −192° (c = 0.345, $CDCl_3$); IR ($CHCl_3$) 3600 (w), 3440 (w), 3000 (s), 2960 (s), 1640 (s), 1570 (s), 1220 (s), 1190 (s), 1030 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 4.1 Hz, 1H), 7.38 (s, 1H), 5.38 (br s, 1H), 5.00 (t, J = 2.5 Hz, 1H), 3.06 (s, 3H), 2.85 (heptet, J = 6.8, 1H), 2.45–2.29 (m, 2H), 1.94 (heptet, J = 6.8 Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.16 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H); 0.70 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 199.5, 164.3, 160.8, 134.9, 119.5, 117.5, 110.2, 73.7, 73.5, 34.8, 33.8, 33.4, 30.0, 29.2, 28.8, 25.8, 18.1, 17.1, 16.5, 16.2, 15.0; high resolution mass spectrum (CI, CH_4) m/z 387.3005 [$(M+H)^+$; calcd for $C_{24}H_{39}N_2O_2$: 387.3011].

Aminoester alkyne (−)-10. A −78 °C solution of oxazolidinone (−)-**9** (25.4 g, 94.3 mmol) in THF (376 mL) was treated with 0.5 M KHMDS in toluene (207 mL, 114 mmol) via a dropping funnel at a rate that maintained an internal temperature of −70 °C. The resultant yellow solution was stirred for 15 min and then treated dropwise with trimethylsilyl propargyl bromide (13.5 g, 113 mmol) in THF (20 mL), again maintaining an internal temperature no higher than −70 °C. The reaction was stirred an additional 30 min at −78 °C and quenched at low temperature (−78 °C) with 10% aqueous $NaHSO_4$ (350 mL). Following extraction with EtOAc (2×350 mL), the combined organic phases were washed with 10% aq $NaHSO_4$, satd aq $NaHCO_3$, and brine (350 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (5% ethyl acetate:hexanes) gave the alkylated oxazolidinone, (25.1 g, 79.3% yield) as a colorless oil: $[\alpha]_D^{20}$ +89.0° (c = 1.0, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2170 (w), 1775 (s), 1705 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddd, J = 17.0, 10.5, 6.2 Hz, 1H), 5.59 (s, 1H), 5.34 (ddd, J = 17.1, 2.9, 1.5 Hz, 1H), 5.25 (ddd, J = 10.4, 2.4, 1.2 Hz, 1H), 4.63 (ddt, J = 12.8, 6.1, 1.1 Hz, 1H), 4.57 (ddt, J = 13.0, 6.2, 1.1 Hz, 1H), 3.28 (br d, J = 16.7 Hz, 1H), 2.74 (d, J = 16.8 Hz, 1H) 2.27 (septet, J = 6.7 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 0.99 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.3, 131.9, 119.2, 100.3, 96.1, 89.4, 69.6, 67.1, 37.5, 35.4, 25.8, 23.7, 18.6, 17.9, −0.2; high resolution mass spectrum (CI, N-H_3) m/z 402.2071 [$(M+Na)^+$; calcd for $C_{20}H_{33}NO_4$SiNa: 402.2076].

A solution of the alkylated oxazolidinone (25.1 g, 74.8 mmol) in a mixture of methanol and 1 N aqueous NaOH (374 mL each) was heated at reflux for 16 h. The resulting solution was cooled to room temperature and concentrated in vacuo, and the resultant mixture was acidified with 10% aqueous $NaHSO_4$ to pH 1 and then extracted with EtOAc (3×500 mL). The combined organic phases were washed with H_2O and brine (500 mL each), dried over $MgSO_4$ and concentrated in vacuo.

A solution of the (crude) residue in DMF (25 mL) was treated with anhydrous K_2CO_3 (25 g), and cooled to 0 °C. Iodomethane (9.32 mL, 150 mmol) was slowly added and the resultant yellow mixture stirred at 0 °C for 30 min and then at room temperature for 30 min. The reaction mixture was quenched with H_2O (100 mL) and extracted with ether (2×500 mL). The combined extracts were washed with H_2O (4×500 mL), sat. aq. $NaHCO_3$ (500 mL), and brine (500 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (10% ethyl acetate:hexanes) gave (−)-**10** (13.3 g, 75% yield) as a clear colorless oil: $[\alpha]_D^{20}$ −19.8° (c = 1.89, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3415 (m), 3310 (m), 3020 (s), 2970 (m), 2400 (w), 2120 (w), 1720 (s), 1500 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90–5.82 (m, 1H), 5.67 (br s, 1H), 5.26 (dd, J = 17.2, 1.4 Hz, 1H), 5.15 (dd, J = 10.5, 1.1 Hz, 1H), 4.50 (d, J = 5.3 Hz, 2H), 3.73 (s, 3H), 3.24 (d, J = 16.8 Hz, 1H), 2.95 (dd, J = 16.9, 2.6 Hz, 1H), 2.38–2.34 (m, 1H), 1.91 (t, J = 2.5 Hz, 1H), 0.92 (apparent t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 154.6, 132.7, 117.3, 79.8, 70.6, 65.7, 65.2, 52.5, 33.5, 23.3, 17.6, 17.5; high resolution mass spectrum (CI, N-H_3) m/z 254.1391 [$(M+H)^+$; calcd for $C_{13}H_{20}NO_4$: 254.1392]. Anal. calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56. Found: C, 61.67; H, 7.60.

Trimethylsilylalkyne amine (+)-11. A solution of diisopropylamine (2.12 mL, 16.2 mmol) in dry THF (17 mL) was stirred at −78 °C, and 1.6 M n-butyllithium (8.43 mL, 13.5 mmol) was added dropwise. The reaction mixture was stirred for 30 min, and then added via cannula to a solution of (−)-**10** and trimethylsilyl chloride (1.71 mL, 13.5 mmol) in THF (22 mL) at −78 °C. The reaction was quenched after 25 min with 10% aqueous $NaHSO_4$ (100 mL), and extracted with EtOAc (2×100 mL). The combined extracts were washed with sat. aq. $NaHCO_3$ and brine (100 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (5% ethyl acetate:hexanes) afforded the silylated alkynyl amino ester (1.49 g, 88% yield) as a clear colorless oil: $[\alpha]_D^{20}$ −14.4° (c = 1.00, $CDCl_3$); IR ($CHCl_3$) 3420 (m), 3010 (m), 2180 (m), 1725 (s), 1505 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92–5.84 (m, 1H), 5.68 (br s), 5.29 (dd, J = 17.2, 1.4 Hz, 1H), 5.17 (dd, J = 10.8, 1.4 Hz, 1H), 4.53 (apparent d, J = 5.2 Hz, 2H), 3.74 (s, 3H), 3.27 (br d, J = 17.0 Hz, 1H), 2.96 (d, J = 17.0 Hz, 1H), 2.40–2.34 (m, 1H) 0.93 (apparent t, J = 7.5 Hz, 6H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 154.5, 132.9, 117.3, 87.4, 66.0, 65.2, 52.5, 33.6, 24.6, 17.7, 17.6, 0.0; high resolution mass spectrum (CI, N-H_3) m/z 326.1796 [$(M+H)^+$; calcd for $C_{16}H_{29}NSiO_4$: 326.1787]. Anal. calcd for $C_{16}H_{28}NSiO_4$: C, 59.04; H, 8.36; N, 4.30. Found: C, 58.82; H, 8.57; N, 4.29.

A mixture of the silylated alkynyl amino ester (3.52 g, 1.14 mmol), dimedone (4.8 g, 3.4 mmol), and $Pd(PPh_3)_4$ (65 mg, 0.057 mmol) in THF (57 mL) was stirred at room temperature for 16 h. Following dilution with ether (150 mL) and extraction with 1 N HCl (5×125 mL), the combined aqueous layers were made basic by careful addition of solid K_2CO_3. Additional base was added to facilitate extraction of the product. The resultant mixture was extracted with EtOAc (3×300 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine (300 mL each), dried over $MgSO_4$, and concentrated in vacuo. Kugelrohr distillation (heat gun, 0.01 mm Hg) provided (+)-**11** (2.49 g, 97% yield) as a colorless oil: $[\alpha]_D^{20}$ −25.5° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 2970 (s), 2900 (w), 2180 (m), 1735 (s), 1435 (m), 1250 (s), 840 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.63 (d, J = 16.4 Hz, 1H), 2.43 (d, J = 16.4 Hz, 1H), 1.94 (sept, J = 6.9 Hz, 1H), 1.69 (s, 2H), 0.88 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 102.6, 87.9, 64.2, 52.1, 35.1, 29.5, 17.9, 16.2, 0.0; high resolution mass spectrum (CI, N-H_3) m/z 242.1568 [$(M+H)^+$; calcd for $C_{12}H_{24}NO_2Si$: 242.1576].

Bispyrrolinone (+)-7. A solution of aldehyde (+)-**3** (1.62 g, 6.39 mmol) in benzene (13 mL) was treated with amine (+)-**11** (1.44 g, 6.39 mmol). After 1.5 h the

solution was concentrated in vacuo, and the residue was azeotropically dehydrated with benzene (7×13 mL) and then subjected to high vacuum overnight. The resultant oil was dissolved in THF (64 mL) and 0.5 M KHMDS in toluene (44.8 mL, 22.4 mmol) was added. This solution was allowed to stir for 15 min and then was quenched with 10% aqueous $NaHSO_4$ (125 mL). The aqueous phase was extracted with EtOAc (2×125 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine (125 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash chromatography (30% ethyl acetate in hexanes) afforded (+)-**7** (1.34 g, 57% yield) as light yellow crystals: mp 89–92 °C (crystallized from ethyl acetate at 0 °C): $[\alpha]_D^{20}$ +324° (c = 1.0, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3310 (m), 3010 (m), 2970 (s), 2940 (m), 2880 (m), 1670 (s), 1650 (s), 1490 (m), 1460 (m), 1365 (m), 1285 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 4.0 Hz, 1H), 7.40 (s, 1H), 5.83 (br s, 1H), 3.05 (s, 3H), 2.85 (m, 1H), 2.64 (dd, J = 16.8, 2.5 Hz, 1H), 2.44 (dd, J = 16.8, 2.5 Hz, 1H), 2.03 (m, 1H), 1.96 (t, J = 2.5 Hz, 1H), 1.16 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 199.4, 164.9, 161.1, 119.5, 109.7, 79.1, 73.5, 71.1, 71.0, 34.8, 33.2, 30.0, 29.1, 29.0, 25.2, 19.6, 16.3 (2C), 15.3; high resolution mass spectrum (CI, N-H_3) m/z 357.2540 [$(M+H)^+$; calcd for $C_{22}H_{33}N_2O_2$: 357.2542]. Anal. calcd for $C_{22}H_{33}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.50; H, 9.11; N, 7.66.

Monopyrrolinone aldehyde (−)-13. At room temperature a solution of amino ester (−)-**2** (2.36 g, 10.8 mmol) in benzene (21 mL) was treated with aldehyde **12** (2.66 g, 10.8 mmol). Condensation was effected by allowing the mixture to stand for 2 h, followed by concentration in vacuo and azeotropic dehydration with additional benzene (7×21 mL). The resultant oil was placed under high vacuum overnight. The resultant oil was then dissolved in THF (105 mL) and 0.5 M KHMDS in toluene (75.4 mL, 37.7 mmol) was added dropwise rapidly at room temperature. The mixture was stirred for 15 min, followed by addition of iodomethane (2.68 mL, 43.1 mmol). After 15 min the reaction was quenched with 10% aqueous $NaHSO_4$ (125 mL), and extracted with EtOAc (2×125 mL). The combined extracts were washed with sat. aq. $NaHCO_3$ and brine (125 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (30% ethyl acetate:hexanes with 1% Et_3N) gave the monopyrrolinone dimethyl acetal (3.87 g, 83% yield) as a clear colorless oil: $[\alpha]_D^{20}$ = +21.1° (c = 0.985, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2960 (s), 2930 (s), 2870 (s), 1650 (s), 1575 (s) 1450 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.61 (s, 1H), 4.03 (dd, J = 6.3, 3.9 Hz, 1H), 3.58–3.54 (m, 2H), 3.50 (dd, J = 10.3, 9.0 Hz, 2H), 3.23 (s, 3H), 3.19 (s, 3H), 2.97 (s, 3H), 2.14 (dd, J = 14.3, 3.8 Hz, 1H), 1.92–1.86 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 0.92–0.89 (m, 2H), 0.88 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 162.9, 116.1, 102.4, 95.2, 75.1, 72.8, 64.8, 54.4, 53.0, 36.8, 34.3, 34.2, 33.8, 24.2, 24.1, 18.1, 16.9, 15.3, −1.4; high resolution mass spectrum (ESI) m/z 452.2793 [$(M+Na)^+$; calcd for $C_{22}H_{43}NO_5SiNa$: 452.2808]. Anal. calcd for $C_{22}H_{43}NO_5Si$: C, 61.50; H, 10.09; N, 3.26. Found: C, 61.21; H, 10.29; N, 3.24.

To a solution of the monopyrrolinone dimethyl acetal (3.87 g, 8.94 mmol) in a 3:1 mixture of THF:water (89 mL) was added TsOH (1.7 mg, 0.089 mmol). The reaction was heated at 55 °C for 1.5 h and was then diluted with Et_2O (200 mL) after being allowed to cool to room temperature. The mixture was washed with sat. aq. $NaHCO_3$ and brine (100 mL each). The organic phase was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (30% ethyl acetate:hexanes) afforded (−)-**13** (3.31 g, 96% yield) as a clear colorless oil: $[\alpha]_D^{20}$ +24.8° (c = 1.0, $CHCl_3$); IR ($CHCl_3$) 3005 (s), 2960 (s), 2880 (s), 1724 (s), 1650 (s), 1580 (s), 1460 (m), 1250 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, J = 5.5 Hz, 1H), 7.55 (s, 1H), 4.59 (s, 2H), 3.54 (m, 3H), 2.96 (d, J = 14.3 Hz, 1H), 2.95 (s, 3H), 2.53 (dd, J = 14.3, 5.6 Hz, 1H), 1.99 (sept, J = 6.9 Hz, 1H), 1.15 (s, 6H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (m, 2H), 0.80 (d, J = 7.0 Hz, 3H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 163.4, 117.4, 95.2, 74.9, 72.5, 64.8, 47.4, 34.3, 33.5, 33.4, 24.2, 24.1, 18.1, 16.4, 15.1, −1.4; high resolution mass spectrum (CI, NH_3) m/z 384.2574 [$(M+H)^+$; calcd for $C_{20}H_{38}NO_4Si$: 384.2569]. Anal. calcd for $C_{20}H_{37}NO_4Si$: C, 62.62; H, 9.72; N, 3.65. Found: C, 62.90; H, 9.93; N, 3.56.

Bispyrrolinone (−)-14. A solution of aldehyde (−)-**13** (3.17 g, 8.19 mmol) in benzene (16 mL) was treated with amine (−)-**4** (1.64 g, 8.19 mmol). Condensation was effected by allowing the mixture to stand for 1.5 h followed by concentration in vacuo and azeotropic dehydration with additional benzene (7×16 mL). The resultant oil was placed under high vacuum overnight. The residue was then dissolved in THF (82 mL) and 0.5 M KHMDS in toluene (57.4 mL, 28.7 mmol) was added rapidly at room temperature. The mixture was stirred for 15 min, followed by addition of allyl chloroformate (3.48 mL, 32.8 mmol). After 15 min the reaction was quenched with 10% aqueous $NaHSO_4$ (125 mL), and extracted with EtOAc (2×125 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine (125 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10% ethyl acetate:hexanes) afforded (−)-**14** (2.94 g, 58% yield) as a clear colorless oil: $[\alpha]_D^{20}$ −170.1° (c = 1.11, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2990 (s), 2950 (s), 2890 (m), 1735 (s), 1695 (s), 1655 (s), 1605 (s), 1580 (s), 1400 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.47 (s, 1H), 5.89 (ddd, J = 17.1, 10.4, 5.5 Hz, 1H), 5.29 (d, J = 17.1 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 4.68 (t, J = 7.0 Hz, 1H), 4.64 (d, J = 5 Hz, 2H), 4.59 (s, 2H), 3.60–3.49 (m, 2H), 3.51 (s, 2H), 3.01 (s, 3H), 2.80–2.65 (m, 3H), 2.50 (br s, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 8.3 Hz, 2H), 0.85 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.66 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 162.9, 162.7, 157.7, 135.7, 131.5, 118.9, 118.4, 116.9, 116.3, 95.2, 76.3, 75.0, 72.8,

66.9, 64.7, 35.0, 34.3, 32.2, 29.2, 25.8, 24.2, 24.1, 18.1, 18.0, 17.2, 16.4, 15.6, 15.4, 15.3, 14.8, −1.45; high resolution mass spectrum (CI, NH_3) m/z 617.3962 [$(M+H)^+$; calcd for $C_{34}H_{57}N_2O_6Si$: 617.3985]. Anal. calcd for $C_{34}H_{56}N_2O_6Si$: C, 66.20; H, 9.15; N, 4.54. Found: C, 66.02; H, 9.21; N, 4.49.

Bispyrrolinone aldehyde (−)-8. To a solution of (−)-**14** (2.87 g, 23.3 mmol) in a 3:1 mixture of methanol:water (47 mL) was added TsOH (4.42 g, 23.3 mmol). The reaction was heated at 55 °C for 1.5 h and was then allowed to cool to room temperature and solvent removed in vacuo. The mixture was diluted with 50% saturated aqueous $NaHCO_3$ and ethyl acetate (100 mL each). The organic phase was then washed with sat. aq. $NaHCO_3$ and brine (100 mL each), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (30% ethyl acetate: hexanes) gave the bispyrrolinone alcohol (2.23 g, 94% yield) as a pale yellow oil: $[\alpha]_D^{20} = +101.1°$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$) 3500 (w), 3250 (br w), 2980 (s), 2910 (m), 1730 (s), 1680 (s), 1600 (s), 1565 (s), 1390 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6 at 348 K) major rotamer δ 8.62 (s, 1H), 7.20 (s, 1H), 5.73–5.64 (m, 1H), 5.13 (ddd, $J = 17.3$, 2.9, 1.5 Hz, 1H), 5.02–4.97 (m, 2H), 4.46 (dt, $J = 5.6$, 1.5 Hz, 2H), 3.84 (d, $J = 10.4$ Hz, 1H), 3.71 (br s, 1H), 3.61 (d, $J = 10.4$ Hz, 1H), 3.04 (br dd, $J = 13.4$, 7.1 Hz, 1H), 2.88 (dd, $J = 14.5$, 7.44 Hz, 1H), 2.70 (s, 3H), 2.66 (septet, $J = 7.1$ Hz, 1H), 1.59 (d, $J = 7.1$ Hz, 6H), 1.22 (d, $J = 10.5$ Hz, 6H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 7.1$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); minor rotamer δ 8.56 (s, 1H), 7.16 (s, 1H), 4.93–4.88 (m, 1H), 4.52 (ddt, $J = 13.4$, 5.6, 1.5 Hz, 1H), 4.42 (ddt, $J = 13.4$, 5.6, 1.5 Hz, 1H), 3.85 (d, $J = 10.4$ Hz, 1H), 3.60 (d, $J = 10.1$ Hz, 1H), 2.81 (dd, $J = 14.9$, 6.7 Hz, 1H), 1.23 (d, $J = 10.4$ Hz, 6H), 1.10 (d, $J = 7.1$ Hz, 3H), 0.90 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6 at 348 K) δ 202.6, 199.4, 163.7, 157.8, 135.7, 132.1, 128.2, 119.1, 118.4, 118.0, 117.4, 76.8, 73.3, 71.9, 66.9, 36.4, 34.6, 34.5, 32.8, 30.1, 25.8, 25.1, 24.7, 18.1, 17.3, 15.9, 15.6, 15.3; high resolution mass spectrum (ESI) m/z 509.2998 [$(M+Na)^+$; calcd for $C_{28}H_{42}N_2O_5Na$: 509.2991]. Anal. calcd for $C_{28}H_{42}N_2O_5$: C, 69.11; H, 8.70; N, 5.76. Found: C, 69.09; H, 8.84; N, 5.75.

A solution of the bispyrrolinone alcohol (317 mg, 0.651 mmol) in DMSO (4 mL) was treated with Et_3N (1.90 mL, 13.7 mmol) followed by a solution of pyr·SO_3 (726 mg, 4.56 mmol) in DMSO (3 mL). The resultant mixture was stirred for 10 min at room temperature, then diluted with ether and water (20 mL each). The combined aqueous phases were washed with ether (20 mL), and the combined organic layers were washed with water (2×20 mL), 10% aqueous $NaHSO_4$ (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (20% ethyl acetate:hexanes) gave (−)-**8** (299 mg, 95% yield) as a clear colorless oil: $[\alpha]_D^{20}$ −122.4° ($c = 2.33$, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2990 (m), 2940 (m), 1730 (s), 1690 (s), 1650 (m), 1595 (s), 1575 (m), 1390 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.25 (br s, 1H), 7.53 (s, 1H), 5.94–5.85 (m, 1H), 5.30 (dd, $J = 17.2$, 1.4 Hz, 1H), 5.24 (dd, $J = 10.4$, 1.1 Hz, 1H), 4.66 (d, $J = 3.9$ Hz, 3H), 3.04 (s, 3H), 2.78–2.64 (m, 3H), 2.49 (br s, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.9$ Hz, 3H), 0.67 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 197.8, 162.9, 162.8, 157.8, 135.8, 131.4, 118.9, 117.6, 116.8, 112.4, 76.4, 73.3, 67.0, 44.6, 34.3, 33.5, 32.2, 29.4, 25.8, 21.1, 21.0, 18.0, 17.1, 16.3, 15.3, 14.7; high resolution mass spectrum (CI, NH_3) m/z 485.3019 [$(M+H)^+$; calcd for $C_{28}H_{41}N_2O_5$: 485.3015].

Tetrapyrrolinone carbinols (−)-15a and (−)-15b. To a solution of alkyne (+)-**7** (228 mg, 0.617 mmol) in THF (4 mL) at −78 °C was added dropwise 1.0 M LiHMDS in THF (1.85 mL, 1.85 mmol). After 5 min, a solution of aldehyde (−)-**8** (299 mg, 0.617 mmol) in THF (2 mL) at −78 °C was transferred via cannula into the reaction. After 15 min, the reaction was quenched with satd aq NH_4Cl (20 mL) and diluted with ethyl acetate (20 mL). The organic layers were then washed with sat. aq. NH_4Cl and brine (20 mL each), dried over $MgSO_4$, and concentrated in vacuo. The residue was filtered through a plug of silica gel (40% ethyl acetate in hexanes) to afford an inseparable mixture of alcohol diastereomers (384 mg, 74% yield).

To a solution of the alcohol diastereomers (384 mg, 0.457 mmol) in THF (4.6 mL) at −78 °C was added 0.5 M KHMDS in toluene (0.913 mL, 0.457 mmol). After 15 min, allyl chloroformate (48.5 μL, 0.457 mmol) was added and the solution was allowed to stir for 15 min. The reaction was quenched with sat. aq. NH_4Cl (25 mL) and diluted with ethyl acetate (25 mL). The aq layer was washed with ethyl acetate (25 mL) and the combined organic layers were washed with satd aq NH_4Cl and brine (25 mL each), dried over $MgSO_4$, and concentrated in vacuo. Purification via flash chromatography (20% ethyl acetate:hexanes) gave the higher R_f diastereomer (−)-**15a** (249 mg, 60% yield) and the lower R_f diastereomer (−)-**15b** (116 mg, 27% yield) as light yellow foams.

Higher R_f diastereomer (−)-15a. $[\alpha]_D^{20}$ −103.5° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3480 (w), 2880 (s), 2840 (s), 1735 (s), 1695 (s), 1655 (s), 1600 (s), 1580 (s), 1470 (s), 1395 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 2H), 7.49 (s, 1H), 7.44 (s, 1H), 5.94 (heptet, $J = 5.7$ Hz, 1H), 5.91 (heptet, $J = 5.7$ Hz, 1H), 5.33 (dddd, $J = 17.2$, 9.5, 2.8, 1.4 Hz, 2H), 5.27 (d, $J = 1.1$ Hz, 1H), 5.25 (d, $J = 1.1$ Hz, 1H), 4.75–4.62 (m, 4H), 4.36 (s, 1H), 3.10 (br s, 1H), 2.90–2.71 (m, 2H), 2.69–2.61 (m, 3H), 2.47 (br s, 2H), 1.15 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.77 (d, $J = 6.9$ Hz, 3H), 0.70 (d, $J = 6.7$ Hz, 3H), 0.69 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 201.4, 198.6, 198.5, 164.4, 162.2, 158.0, 135.8, 131.6, 120.3, 119.0, 118.5, 116.8, 116.3, 83.4, 78.4, 76.4, 73.1, 68.8, 67.2, 39.1, 35.3, 34.6, 33.7, 33.1, 33.0, 32.2, 30.3, 29.9, 29.7, 29.6, 29.0, 25.9, 25.0, 23.8, 22.4, 18.0, 17.3, 17.1, 16.9, 15.5, 15.4, 15.1, 14.9; high resolution mass spectrum (FAB,

NBA) m/z 925.5683 [$(M+H)^+$; calcd for $C_{54}H_{77}O_9N_4$: 925.5690].

Lower R_f diastereomer (−)-15b. $[\alpha]_D^{20}$ 142.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3250 (br w), 2980 (s), 2940 (m), 1740 (s), 1700 (s), 1655 (m), 1600 (s), 1580 (s), 1395 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.24 (s, 1H), 7.49 (s, 1H), 7.45 (s, 1H), 5.96–5.86 (m, 2H), 5.36 (d, $J=1.1$ Hz, 1H), 5.32 (dd, $J=3.0$, 1.3 Hz, 1H), 5.29 (s, 1H), 5.27 (t, $J=1.1$ Hz, 1H), 5.24 (d, $J=0.9$ Hz, 1H), 4.67 (br d, $J=5.6$ Hz, 4H), 3.91 (s, 1H), 3.07 (s, 3H), 3.00 (s, 3H), 2.71–2.66 (m, 3H), 2.67 (heptet, $J=6.7$ Hz, 1H), 2.49 (br s, 1H), 2.39 (br s, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.17 (s, 3H), 1.14 (s, 9H), 1.11 (s, 3H), 1.00 (d, $J=6.9$ Hz, 3H), 0.91 (t, $J=7.0$ Hz, 6H), 0.88 (t, $J=6.7$ Hz, 6H), 0.82 (d, $J=6.8$ Hz, 3H), 0.68 (d, $J=6.9$ Hz, 3H), 0.66 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 200.8, 199.2, 198.2, 165.0, 157.5, 135.9, 131.4, 120.1, 118.9, 117.2, 116.9, 116.8, 116.4, 83.7, 78.1, 76.5, 74.1, 74.0, 73.1, 72.0, 67.1, 66.8, 39.8, 35.8, 35.5, 33.1, 32.1, 30.7, 29.9, 29.7, 29.0, 25.9, 25.2, 24.7, 18.1, 17.3, 17.1, 17.0, 16.5, 15.4, 15.3, 15.2, 14.9; high resolution mass spectrum (FAB, NBA) m/z 925.5691 [$(M+H)^+$; calcd for $C_{54}H_{77}O_9N_4$: 925.5690].

Tetrapyrrolinone (−)-6. A solution of (−)-**15a** (103 mg, 0.111 mmol) in THF (2 mL) was cooled to −78 °C and treated with LiHMDS (1.0 M in THF, 133 μL, 0.133 mmol). After 10 min carbon disulfide (13.3 μL, 0.222 mmol) was added, and the solution was allowed to stir at −78 °C for 45 min. Methyl iodide was then added (25 μL, 0.39 mmol) and the solution was allowed to stir at −78 °C for 45 min and then at room temperature for 45 min. The solvent was then removed in vacuo and the crude xanthate was filtered through a plug of silica gel (30% ethyl acetate:hexanes with 1% Et_3N) and was used in the next step without further purification.

Triphenyltin hydride (227 mg, 0.647 mmol) was added to a solution of the crude xanthate (113 mg, 0.108 mmol) in benzene (3.4 mL). The solution was cooled to 10 °C and Et_3B (1M in hexanes, 108 mL, 0.108 mmol) was added. The solution was allowed to stir for 10 min, and was then diluted with Et_2O (25 mL) and washed with 10% NaOH (25 mL). The aqueous layer was washed with Et_2O (25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Gradient flash chromatography (5→10→20% ethyl acetate:hexanes) gave the *N*-Alloc tetrapyrrolinone (83.5 mg, 85% yield) as a pale yellow foam: $[\alpha]_D^{20}$ 155.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2940 (m), 1730 (s), 1695 (s), 1650 (s), 1600 (s), 1580 (s), 1405 (s), 1395 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.21 (br s, 1H), 5.96–5.85 (m, 2H), 5.34 (dd, $J=17.2$, 1.2 Hz, 2H), 5.25 (apparent ddd, $J=17.2$, 8.0, 1.1 Hz, 2H), 4.73–4.65 (m, 4H), 3.01 (s, 3H), 3.00 (s, 3H), 2.96 (d, $J=3.2$ Hz, 1H), 2.77 (br s, 1H), 2.71–2.61 (m, 4H), 2.50 (d, $J=16.2$ Hz, 1H), 2.43 (br s, 1H), 2.09 (d, $J=16.3$ Hz, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.15 (s, 9H), 1.12 (s, 3H), 1.10 (s, 3H), 1.00 (d, $J=7.0$ Hz, 3H), 0.93 (d, $J=7.1$ Hz, 3H), 0.91 (d, $J=6.9$ Hz, 3H), 0.84 (d, $J=6.8$ Hz, 3H), 0.83 (d, $J=6.9$ Hz, 3H), 0.75 (d, $J=7.0$ Hz, 3H), 0.68 (d, $J=6.9$ Hz, 3H), 0.67 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 198.3, 198.0, 162.4, 162.0, 157.5, 135.7, 131.5, 120.2, 118.8, 118.3, 117.5, 116.9, 81.4, 76.2, 75.0, 74.4, 73.0, 72.9, 66.9, 35.4, 35.1, 33.5, 33.1, 30.4, 30.2, 29.9, 29.5, 29.0, 26.3, 26.0, 25.9, 18.0, 17.5, 17.4, 17.1, 16.8, 16.5, 15.5, 15.4, 15.2, 15.1, 14.8; high resolution mass spectrum (FAB, NBA) m/z 931.5567 [$(M+Na)^+$; calcd for $C_{54}H_{76}O_8N_4Na$: 931.5561].

To a solution of the *N*-Alloc tetrapyrrolinone (84 mg, 0.092 mmol) in CH_2Cl_2 (4 mL) was added one drop of water and a catalytic amount of $(Ph_3P)_4Pd$. Bu_3SnH (54 mL, 0.20 mmol) was then added quickly and in one portion via syringe, and vigorous gas evolution was observed along with a darkening of the color of the reaction. The reaction was allowed to stir for 30 min and then concd in vacuo. Flash chromatography (40% ethyl acetate:hexanes) afforded (−)-**6** (65 mg, 96% yield) as light-yellow crystals: mp 211–212 °C (crystallized from acetonitrile at room temperature): $[\alpha]_D^{20}$ −312.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3455 (w), 3250 (w), 2980 (m), 1650 (s), 1580 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, $J=4.2$ Hz, 1H), 7.82 (d, $J=4.2$ Hz, 1H) 7.45 (s, 1H), 7.37 (s, 1), 6.62 (br s, 1H), 5.92 (br s, 1H), 4.96, (m, 1H), 3.05 (s, 3H), 3.03 (s, 1H) 2.86 (apparent sep, $J=6.9$ Hz, 1H), 2.71 (apparent sep, $J=6.9$ Hz, 1H), 2.64 (m, 1H), 2.52 (m, 1H), 2.35 (m, 1H), 2.25 (m, 1H), 2.08 (apparent sep, $J=6.9$ Hz, 1H), 1.91 (apparent sep, $J=6.9$ Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16 (s, 9H) 0.94 (s, 3H), 0.93 (s, 3H), 0.87 (dd, $J=10.7$, 6.9 Hz, 6H), 0.69 (dd, $J=11.0$, 6.9, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 202.8, 199.5, 199.3, 164.7, 164.6, 162.4, 160.8, 134.7, 119.5, 117.6, 116.3, 109.4, 108.6, 81.9, 76.0, 74.0, 73.7, 73.6, 71.4, 35.1, 34.6, 33.9, 33.5, 33.4, 33.1, 31.5, 30.0, 29.6, 29.1, 28.6, 27.0, 26.9, 25.9, 18.1, 17.1, 16.9, 16.6, 16.4, 16.1, 15.2, 15.1; high resolution mass spectrum (FAB, NBA) m/z 763.5152 [$(M+Na)^+$; calcd for $C_{46}H_{68}N_4O_4Na$: 763.5139].

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6. Acetal (−)-**2** was prepared from (−)-**4** in 80% overall yield via amine protection (Cbz) followed by ozonolysis, acetalization, and Cbz removal.

7. Compound (−)-**1** crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k = odd) with a = 10.199(3) Å, b = 10.678(2) Å, c = 11.299(1) Å, β = 101.88(1)°, V = 1196.7(4) Å^3, Z = 2. Oxygens and nitrogens are depicted in red and blue respectively. See supplementary material for complete X-ray data.

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10. Aldehyde **12** was prepared in four steps from methyl isobutyrate in 62% overall yield via a four-step procedure; alkylation of methyl isobutyrate (LDA, THF, −78 °C; prenyl bromide, DMEU), reduction ($LiAlH_4$, CH_2Cl_2), hydroxyl protection (SEMCl, DIPEA), and ozonolysis.

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15. A single level in the packing diagram for (+)-**7** is depicted in Figure 6. There is a second level translated by 1/3, 2/3, 2/3 and a third at 2/3, 1/3, 1/3 due to the centering of the rhombohedral cell. Compound (+)-**7** crystallizes in the rhombohedral (hexagonal) space group R3 (systematic absences hkl: −h + k + l = 3n) with a = 18.9820(3) Å, c = 19.4550(4) Å, V = 6070.8(2) Å^3, Z = 9. Oxygens and nitrogens are depicted in red and blue, respectively. See supplementary material for complete X-ray data.

16. Compound (−)-**6** crystallizes in the triclinic spaces group P1 with a = 11.4980(6) Å, b = 12.7320(7) Å, c = 9.0970(4) Å, α = 108.860(3)°, β = 110.560(3)°, γ = 93.047(3)°, V = 1158.9(1) Å^3, Z = 1. Oxygens and nitrogens are depicted in red and blue, respectively. See supplementary material for complete X-ray data.

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18. The concentration range over which the intermolecular interactions would be minimal was determined by plotting log [(−)-**1**] versus the chemical shift of the NH in ring **d** for each solvent systems. The resultant plot indicated that no intermolecular hydrogen bonding occurs below 0.001 M.

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21. We would like to thank Dr. Clemens Anklin of Bruker Instruments Inc., Billerica, MA for obtaining the NOESY spectra of compound (−)-**6**.

22. The distance obtained from the X-ray structure for the propargylic protons (1.817 Å) was used as the standard distance in the NOE distance calculation: $R = R_{ref}(I_{ref}/I)^{1/6}$; R is the atomic distance and I is intensity.

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25. *Materials and Methods.* All reactions were carried out under argon with dry, freshly distilled solvents, vacuum-flamed glassware, and magnetic stirring, unless otherwise stated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone, benzene and toluene were distilled from sodium, and dichloromethane (CH_2Cl_2) from calcium hydride. Triethylamine, diisopropylethylamine and pyridine were distilled from calcium hydride and stored over KOH. Dimethylsulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves. *n*-Butyllithium and cyclohexylmethyllithium were standardized by titration with diphenylacetic acid. All reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents and E. Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. All melting points were obtained on a Thomas–Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin–Elmer Model 283B spectrophotometer. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer; carbon-13 NMR spectra were recorded on a Bruker WH-250 or WH-500 instrument. Chemical shifts are reported in δ values relative to tetramethylsilane. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter in the solvent indicated. High resolution mass spectra were obtained

at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. High performance liquid chromatography was performed on a Ranin system equipped with a Dynamax Method Manager, Rabbit MPX solvent delivery system, Rheodyne injector, and Gilson Model 131 refractive index detector or Gilson Model 115 variable-wavelength UV detector. The columns employed were 4.0, 10.0 or 25.0 mm×25 cm with 8-μ (60 Å) normal-phase packing. X-ray data were collected on a Rigaku AFC7R automated diffractometer using Cu-K_α radiation; $\lambda = 1.54184$ Å-compound (−)-**1** and on a Rigaku R-AXIS IIc area detector using Mo-K_α radiation; $\lambda = 0.71069$ Å-compounds (−)-**6** and (+)-**7**. The variable temperature studies were performed with the samples in sealed tubes on a Bucher 500 MHz NMR. The desired temperature was achieved by cooling the probe with N_2 gas, with attenuation of the temperature by the probe heater. Samples were allowed to equilibrate at each temperature for 15 min, then the X, Y, Z, Z^2 and Z^3 shims adjusted. Variable concentration experiments were done on the same instrument. The most concentrated sample was prepared first; subsequent concentrations were reached via serial dilution. All shims were adjusted at each concentration. IR measurements were performed on a Perkin–Elmer 1600 Series FT-IR. Spectra were taken using NaCl plates with a path length of 1.0 mm. Microanalyses were performed by Dr. Rakesh K. Kohli at the University of Pennsylvania.