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The Design and Synthesis of 2,5-Linked Pyrrolinones. A Potential Non-Peptide Peptidomimetic Scaffold

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Abstract—The de novo design and initial synthetic studies directed toward construction of a novel non-peptide scaffold for β-strand/sheet and related secondary peptide structural mimics are described. The scaffold, consisting of a repeating array of 2,5,5-trisubstituted pyrrolinone (enaminone) units punctuated with appropriate amino acid side chains, is conceptually related to our previously successful 3,5-linked polypyrrolinone non-peptide peptidomimetic scaffold. Construction of the 2,5,5-trisubstituted pyrrolinone ring system proceeds via intramolecular condensation of an N-protected amino dione. The latter is prepared from a protected α-amino ketone and aldehyde via an aldol–oxidation reaction sequence. Copyright © 1996 Elsevier Science Ltd

Introduction

Since the late 1980s, we have engaged in the design and synthesis of molecules embodying novel scaffolds to replace the polyamide backbone of bioactive peptides, with emphasis not only on increasing stability to proteases, but also improving their pharmacokinetic properties.[1] We took two different approaches: for protease inhibitors (e.g., renin and the HIV-1 protease), we modified the peptide backbone to maintain both side chain spacial orientation and, importantly, the donor and acceptor hydrogen bonding capability of the backbone;[2] for molecules targeted at receptors (e.g., SRIF agonists, and SP and fibrinogen antagonists), we replaced the peptide backbone without regard for backbone hydrogen bonding potential, and concentrated only on the three-dimensional orientations of the requisite peptide side chains.[1c,3] Successful scaffolds that satisfy the latter criteria include the β-D-glucose[4] and the cyclopentanoperhydrophenanthrene (steroid) frameworks.[5]

For enzyme inhibitors, we initially chose to mimic the extended β-strand conformation since crystallographic studies[6] established that proteolytic enzymes, such as the aspartic acid and serine proteases, bind both substrates and inhibitors as β-pleated sheets. In both parallel and antiparallel β-sheets (Fig. 1), the amino acid side chains of individual strands are directed orthogonal to the surface of the sheet, with adjacent side chains on the same strand disposed antiperiplanar. The binding energy derives from a combination of side-chain hydrophobic/hydrophilic interactions and intermolecular hydrogen bonding with the enzyme.[7,8] A successful β-strand mimic thus must incorporate not only the appropriate side-chain trajectories, but also permit intermolecular hydrogen bonds with the complementary strand.[9]

Our interest in protease inhibitors led us initially to the construction of a backbone mimic comprised of 3,5-linked polypyrrolinones, which we incorporated into non-peptide peptidomimetics that adopt the β-strand conformation, both in the solid state[10a,c] and in solution (non-participating solvents).[10d,11] Importantly, the spatial orientation of the backbone carbonyls and amino acid side chains of this novel scaffold closely match those of the corresponding peptide in the solid state, where the pyrrolinone NH protons were also

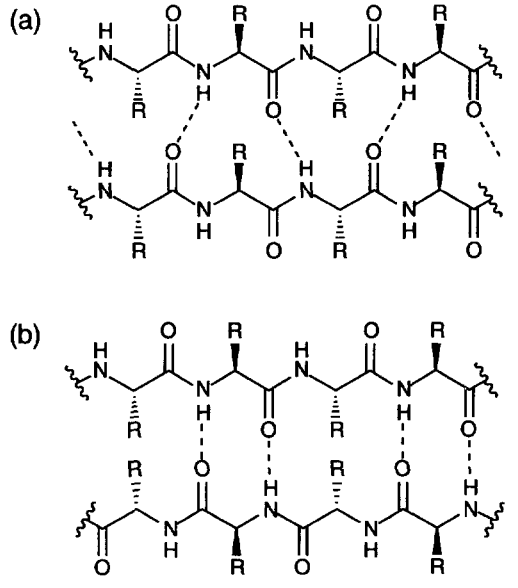


Figure 1. Interstrand H-bonding pattern in (a) parallel and (b) antiparallel β-pleated sheets.

seen to form both intra- and interstrand hydrogen bonds.[10a,c] The intrastrand NH hydrogen bonds involved six-membered rings with the carbonyls of adjacent pyrrolinone rings, leading to an extended linear conformation. The NH units, while displaced from the backbone, also exhibited the propensity to form intermolecular hydrogen bonds with the carbonyls of neighboring pyrrolinone strands. The fact that we were able to prepare both inhibitors of renin and the HIV-1 protease strongly supports our conclusion that the pyrrolinone scaffold can readily form β-pleated sheets with the proteases via a combination of intermolecular H-bonds and hydrophobic interactions.[12]

In this account, we disclose the design and initial synthetic studies directed toward the development of a new scaffold, comprised of an array of 2,5-linked pyrrolinones, as prelude to the study of their conformational properties and their potential use as β-strand mimetics and protease inhibitors.

Background

Initial design of the 3,5-linked pyrrolinone scaffold

The design of the 3,5-linked pyrrolinone scaffold began by first selecting an appropriate replacement for the peptide bond. The enaminone functionality (Fig. 2) was an attractive alternative to the amide functionality for four reasons: (1) the amide and enaminone nitrogens are of similar basicity;[13] (2) the nitrogen and carbonyl moieties possess similar hydrogen bond donor/acceptor capabilities; (3) vinylogous amides are not subject to proteolytic hydrolysis; and (4) the olefin provides an element of preorganization.[14]

Given the lack of atom for atom correspondence between the hydrogen bond donors and acceptors of amides and vinylogous amides, careful attention to the placement of the enaminone unit in the new backbone would be required. To facilitate the eventual synthesis of potential peptidomimetics, we also sought a design strategy that would permit iterative construction like that of the peptides themselves. Thus, starting with a peptide in an extended β-strand conformation (Fig. 3), the amide nitrogens were displaced from the backbone (**2**), the enaminone functionality incorporated at the site vacated by the nitrogens (**3**), and the nitrogens

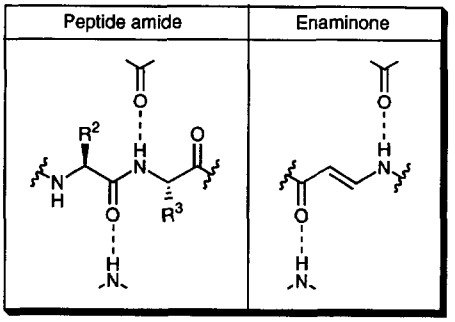


Figure 2. Contrast of the amide and enaminone functionality.

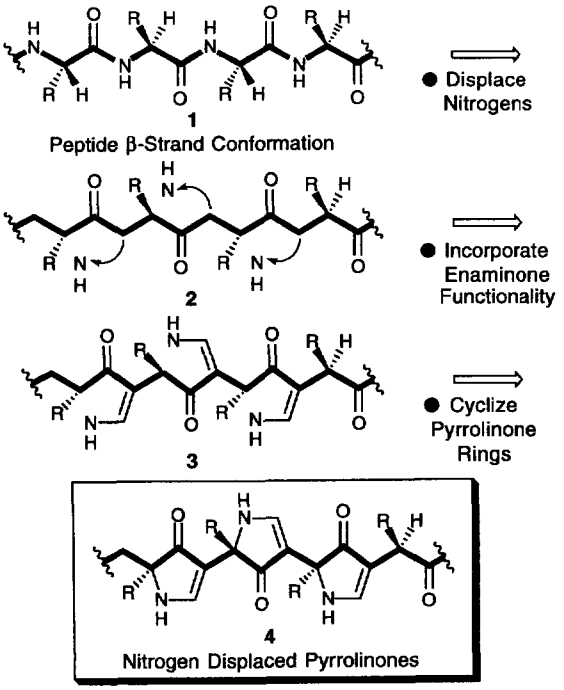


Figure 3. Conceptualization of the 3,5-linked pyrrolinone-based β-sheet mimics.

reconnected to the α-carbon of the backbone to generate the 3,5-linked pyrrolinone framework (**4**).

Design of the 2,5-linked pyrrolinone scaffold

It was readily apparent that displacing the carbonyl moieties of an extended peptide strand instead of the NHs would generate a similar pyrrolinone scaffold (**5**, Fig. 4). Incorporation of the enaminone functionalities (**6**) and reconnection of the displaced carbonyls to the backbone α-carbons would, in this case, afford 2,5-linked pyrrolinones (**7**). Despite the fact that the newly generated backbone is based on the same pyrrolinone heterocycle, unique conformational, chemical, and biological properties could be anticipated. For example, the 2,5-linked polypyrrolinone framework is comprised of a heteroatom backbone, while the backbone of the 3,5-linked polypyrrolinone scaffold is all carbon. Further comparison reveals that the heterocyclic rings of the two scaffolds occupy different registrations relative to the pleats of the β-strand (Fig. 5). We envisioned this structural difference to be of considerable utility. For example, nitrogen-displaced polypyrrolinones could be exploited to interact with macromolecules known to form important hydrogen bonds with the carbonyls of the peptide backbone, rather than the backbone amide NHs. Conversely, we hope to employ carbonyl-displaced pyrrolinones in cases where hydrogen bonding to the NH of the protein is particularly important.

We elected to investigate first the nitrogen-displaced heterocycles since the cross-conjugated relationship between the adjacent enaminone functional units (Fig. 6) suggested that they would not be susceptible to

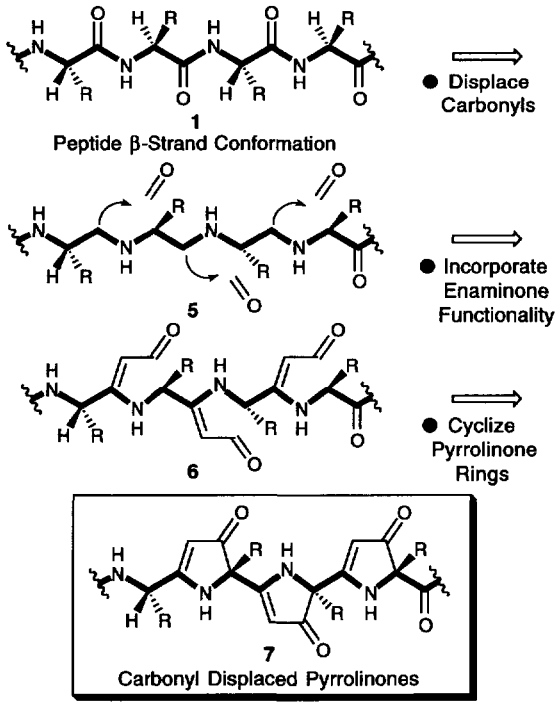


Figure 4. Design of a β-strand mimetic composed of carbonyl displaced 2,5-linked pyrrolinones.

nucleophilic fragmentation, a potential pitfall of the carbonyl-displaced pyrrolinone enaminones. The latter, however, offer compensating advantages (vida infra).

β-Sheet mimic and inhibitor design exploiting the 2,5-linked pyrrolinone scaffold

We designed **8** and **9** (Fig. 7), the 2,5-linked pyrrolinone analogues of our 3,5-linked pyrrolinone β-sheet mimic **12** and our HIV-1 protease inhibitor **13**, to permit direct comparison of the physical and biological properties of the 2,5- and 3,5-linked pyrrolinone based scaffolds with each other and with their peptidal counterparts (**10** and **11**).[15]

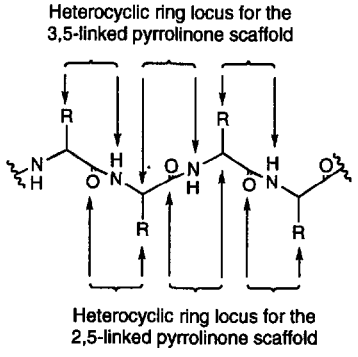


Figure 5. Top view of a β-strand showing the shift in registration of the heterocyclic rings relative to the pleats in the 3,5- and 2,5-linked pyrrolinone frameworks.

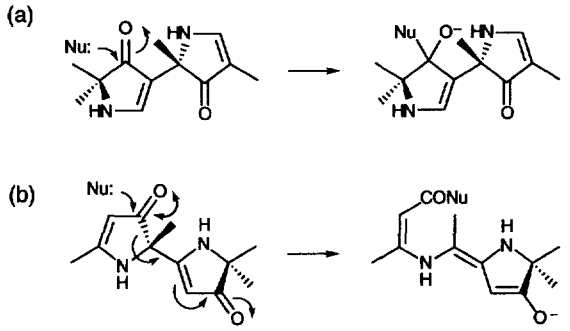


Figure 6. Anticipated susceptibility to nucleophilic attack of (a) 3,5-linked nitrogen-displaced polypyrrolinone scaffolds vs (b) 2,5-linked carbonyl-displaced.

Modeling Studies

The number of degrees of freedom available to a 2,5-linked bis-pyrrolinone, as with a 3,5-linked bis-pyrrolinone, is significantly reduced relative to a dipeptide. For example, in bis-pyrrolinone **14**, the ϕ and ω bonds, which are part of the heterocycles, are locked at 180°. Only the ψ bond is free to rotate. Calculation of the free energy of rotation about the 2,5-bond using the MM2 force field reveals that, unlike the corresponding 3,5-linked **15**,[10c] there are only two minima (Fig. 8). The minimum found at 310° for the nitrogen displaced mimetic **15** has no counterpart in **14**. The lower energy minimum of **14** occurs at 210°, compared to 205° for the 3,5-linked system,[10c] whereas for **15** the higher energy minimum occurs at 120°, compared to 80°. As a result, we predict that mimetics embodying carbonyl displaced pyrrolinones should have a greater propensity to form extended linear conformations than their nitrogen displaced counterparts.

These expectations were confirmed by a Monte Carlo conformational search,[16,17] which revealed only an extended (linear) backbone conformation for **16** (Fig. 9a), whereas three conformations (linear, turn, and twist) had been found for **17** (Fig. 9b).[10c] In addition, this linear conformation of **16** should contain intramolecular six-membered ring hydrogen bonds between the carbonyls of the pyrrolinone rings and the N–H hydrogens of adjacent heterocycles (Fig. 10), similar to the intramolecular hydrogen bonding observed in the 3,5-linked pyrrolinones.[10c] Thus, these studies suggest that the carbonyl displaced pyrrolinones should not only adopt a β-strand conformation in the solid state, but may show a greater tendency, even in aqueous solution, to form a linear strand conformation than their nitrogen displaced pyrrolinone counterparts.[10d]

To validate further the selection of **9** as a potential HIV-1 protease inhibitor, we generated an initial conformation of **9**, analogous to the bound conformation of HIV-1 protease inhibitor MVT-101, as determined by Wlodawer.[18] Energy minimization with the MM2 force field[19] furnished a local minimum (Fig. 11a), which was similar to the initial conformation. Least-squares comparisons with the solid-state conformation of enzyme-bound MVT-101 (Fig. 11b)

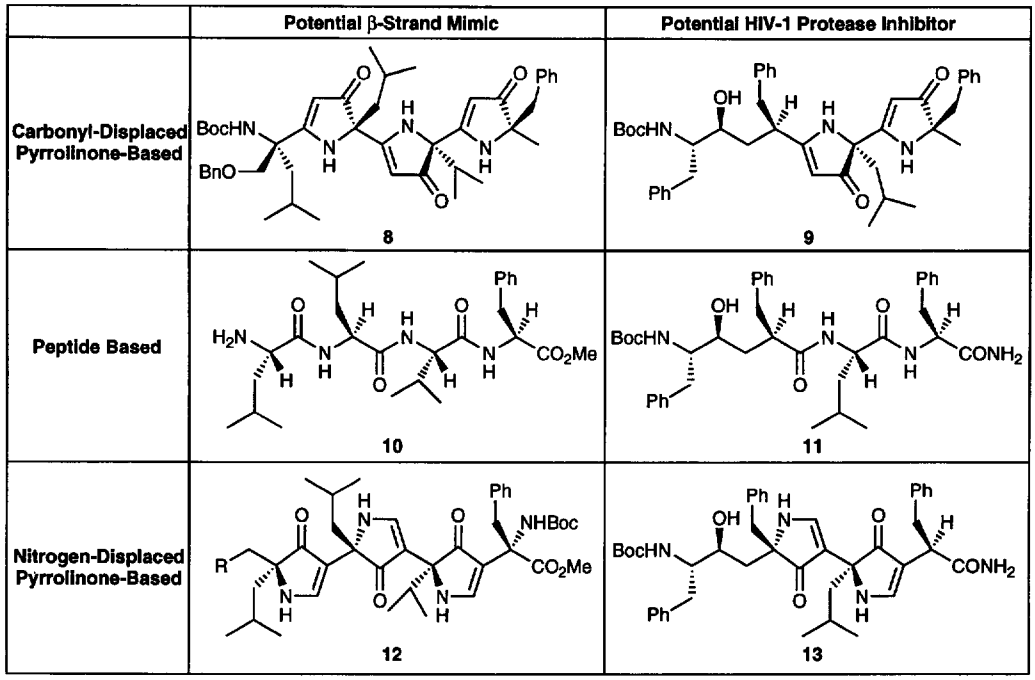


Figure 7. Comparison of the 2,5-linked pyrrolinone peptidomimetics with their 3,5-linked pyrrolinone and petidal counterparts.

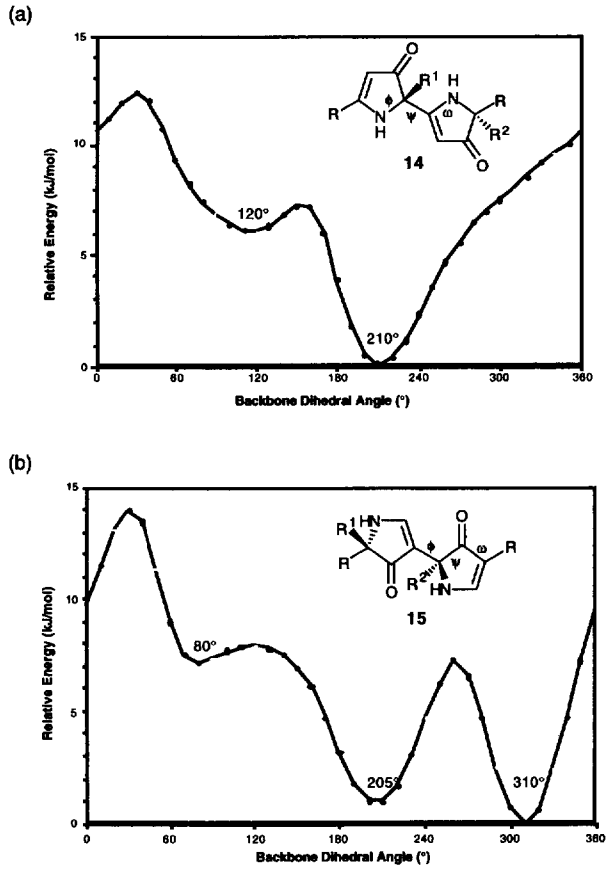


Figure 8. Comparison of a 2,5-linked bis-pyrrolinone **14** and a 3,5-linked bis-pyrrolinone **15**. (a) Energy associated with rotation about ψ of **14** ($R_1 = R_2 = Me$, $R = CHMe_2$) at 10° resolution. (b) Energy of rotation about ϕ of **15** ($R_1 = R_2 = Me$, $R = CHMe_2$) at 10° resolution.

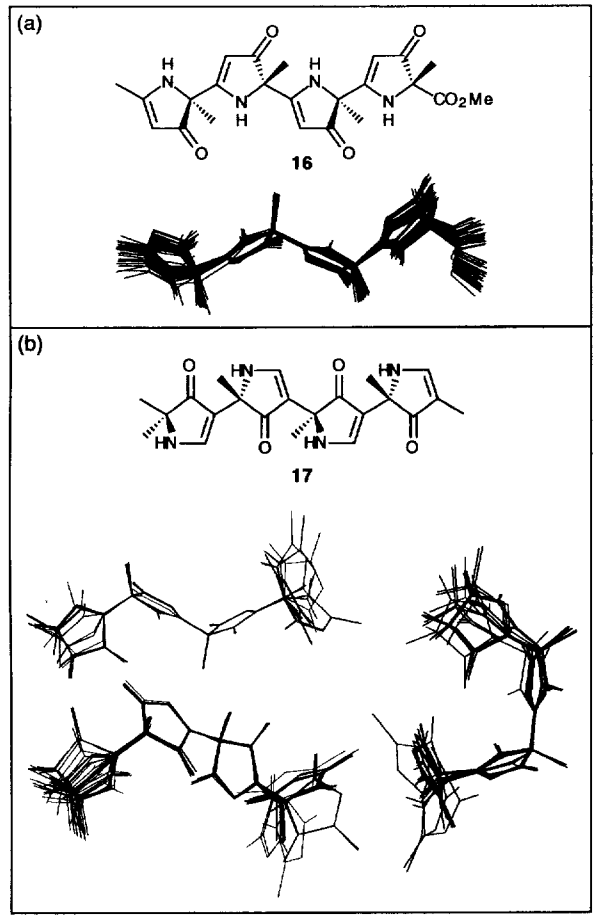


Figure 9. (a) Single predominant backbone conformation found for 2,5-linked tetra-pyrrolinone **16**. (b) Three predominant backbone conformations found for 3,5-linked tetra-pyrrolinone **17**.

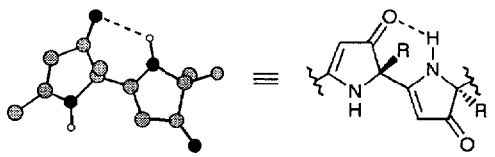


Figure 10. Six-membered ring hydrogen bond between adjacent pyrrolinones in **16**.

indicated that **9** can easily adopt the conformation required for binding. Importantly, docking **9** into the HIV protease active site[20] (Fig. 12) did not reveal any major deleterious steric interactions caused by the increased steric bulk of the heterocyclic rings. Importantly, hydrogen bonding interactions between the N—H hydrogens of **9** and the enzyme were possible and resembled the bonding modes of MVT-101. The pyrrolinone carbonyls, however, did not appear to be positioned appropriately to hydrogen bond with the N—H moieties of the protease. Thus, not unexpectedly, the nitrogen- and the carbonyl-displaced pyrrolinones appear to complement each other in their H-bonding capabilities.

Synthetic Plan

Our approach to the 2,5,5-trisubstituted pyrrolinone ring system is outlined in Scheme 1. Disconnection of the carbon–nitrogen bond of the pyrrolinone ring leads to dione **19**, which we envisaged could be constructed by an aldol–oxidation sequence between ketone **20** and aldehyde **21**.[21]

Extension of this analysis to polypyrrolinone **22** indicated the potential for iterative construction via either 'C-terminal' or 'N-terminal' chain extension (Scheme 2). N-Terminal disconnection (path a) generates ketone **23** and aldehyde **25**, the latter accessible by deprotection and oxidation of the corresponding N-terminal primary alcohol. Repetition of this sequence in retrosynthetic fashion would afford monopyrrolinone **27**; similar disconnection of **27** would then lead to ketone **23** and aldehyde **28**. C-Terminal disconnection (path b) provides ketone **24** and aldehyde **26**; repetition of this disconnection also furnishes **27**.

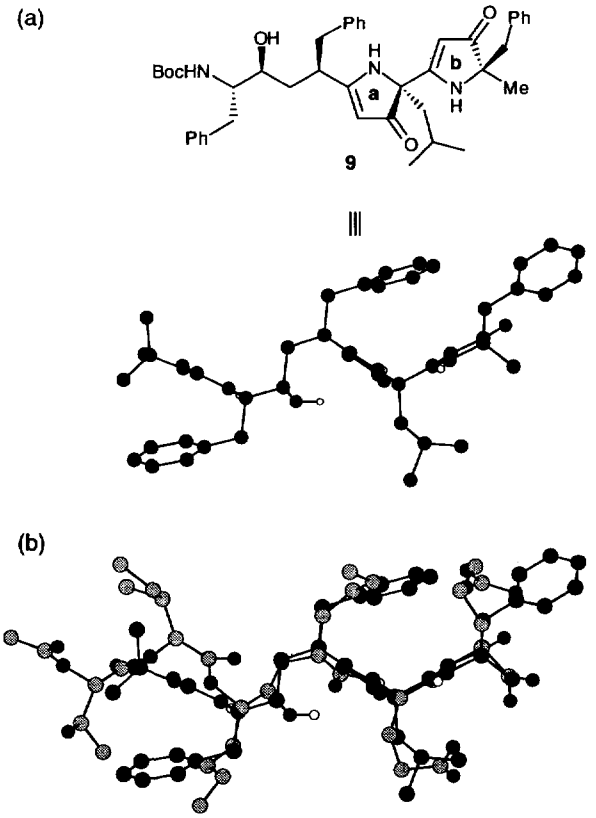


Figure 11. (a) MM2 minimized conformation of HIV1 inhibitor **9**. (b) Comparison of **9** (black) with the HIV-1 co-crystallized inhibitor MVT-101 (gray).

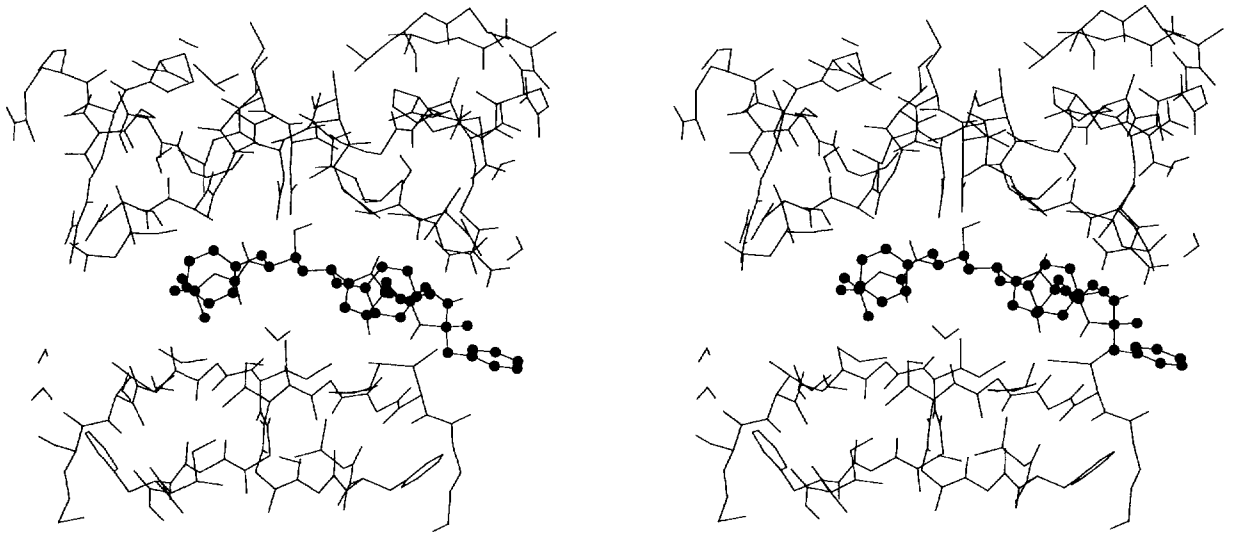
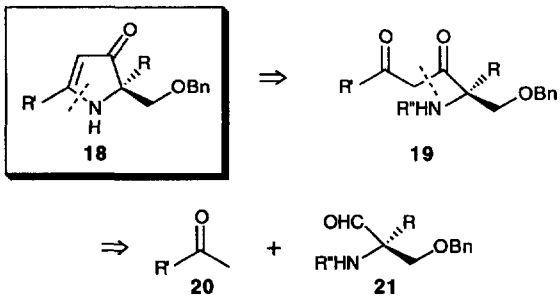


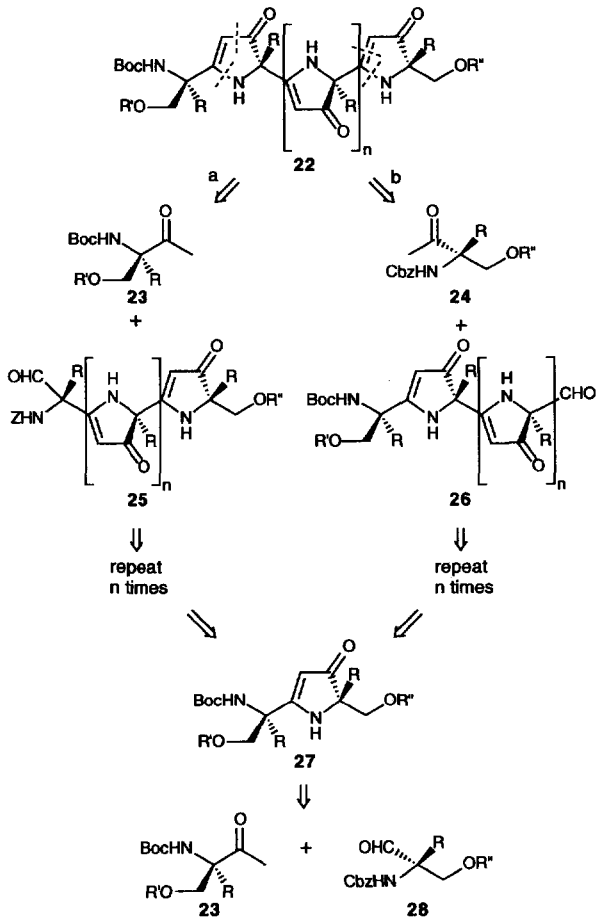
Figure 12. Stereo view of HIV-1 inhibitor peptidomimetic **9** (ball and stick) docked into HIV-1 protease active site (fine lines).



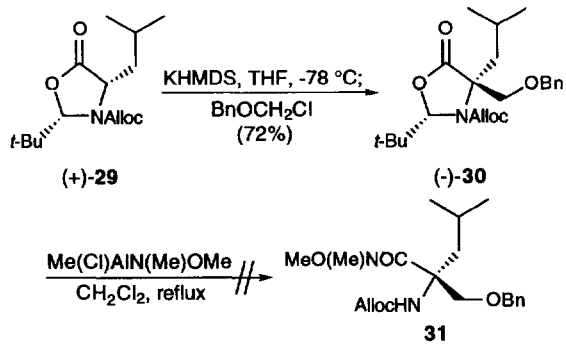
Scheme 1.

The requisite pyrrolinone building blocks

The strategy outlined above required an efficient preparation of α-alkylated, amino-protected ketones and aldehydes such as **23** and **28**, amenable to incorporation of the appropriate peptidal side chains. As with the nitrogen displaced pyrrolinones, we planned to prepare the requisite ketones and aldehydes via the Seebach/Karady oxazolidinones.[22] To this end, treatment of the potassium enolate of (+)-**29** with benzyloxymethyl chloride furnished alkylated oxazolidinone (−)-**30** (Scheme 3) in 72% yield. The benzyl ether moiety was selected to protect the latent aldehyde unit required for subsequent iteration. We initially sought



Scheme 2.

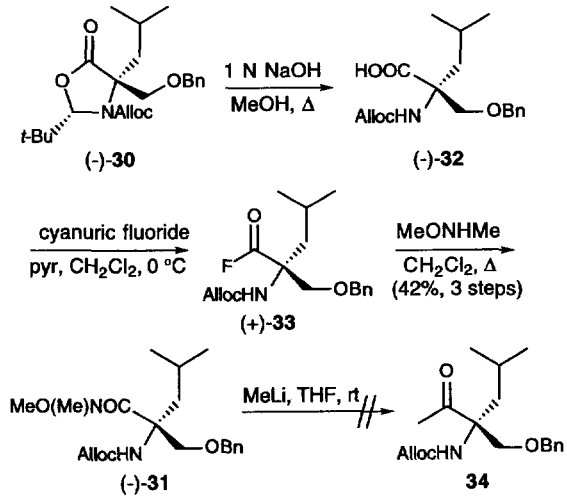


Scheme 3.

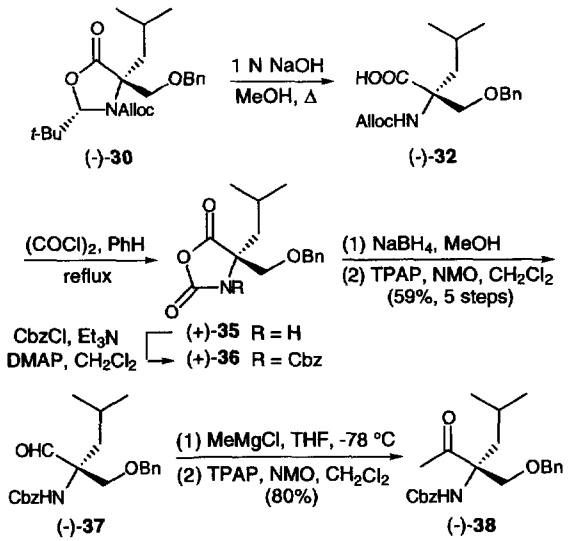
to prepare the desired ketone via the Weinreb amide. Treatment of oxazolidinone (−)-**30** with Me_3Al/MeONHMe,[23] however, afforded only recovered **30**.

We next attempted to obtain amide **31** from the corresponding acid. Hydrolysis of (−)-**30** provided acid (−)-**32** (Scheme 4), which unfortunately could not be converted to the amide **31** through the intermediacy of several mixed anhydrides. It appeared that the desired anhydrides were indeed being formed, but attack of the amine occurred exclusively at the less hindered carbonyl. Amide **31** was eventually prepared by treating acid (−)-**32** with cyanuric fluoride to generate acid fluoride (+)-**33**,[24] which in turn was converted to amide (−)-**31** by exposure to MeONHMe. Unfortunately, treatment of **31** with methyllithium did not afford desired ketone **34**, even at room temperature.

The requisite aldehyde and ketone were ultimately constructed via the *N*-carboxy (Leuchs) anhydrides (Scheme 5). To this end, acid (−)-**32** was treated with oxalyl chloride in benzene at reflux[25] to furnish cleanly Leuchs anhydride (+)-**35**. Protection of the nitrogen as the benzyl carbamate,[26] followed by $NaBH_4$ reduction of the anhydride and subsequent oxidation of the primary alcohol with TPAP/NMO[27] provided aldehyde (−)-**37** in 59% overall yield from **30**. Conversion of



Scheme 4.



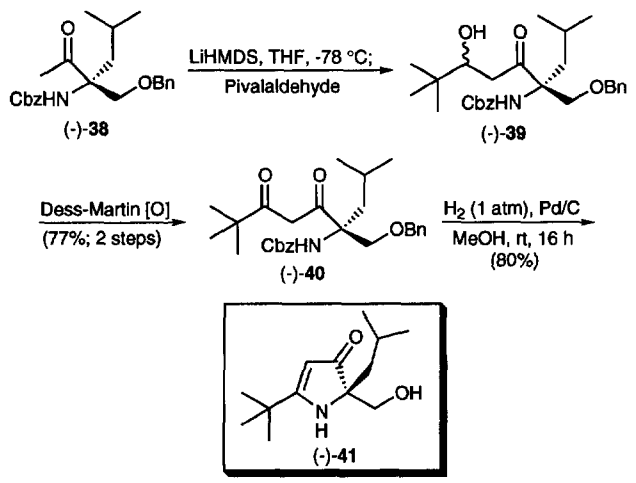
Scheme 5.

aldehyde (−)-**37** to ketone (−)-**38** was then accomplished in two steps (80% yield) by addition of methyllithium and oxidation (TPAP and NMO) of the derived secondary alcohol.

Construction of a 2,5,5-substituted monopyrrolinone

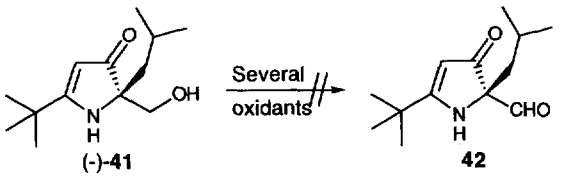
With an efficient synthetic route to the building blocks in hand, we turned to construction of the pyrrolinone ring. We explored first C-terminal extension of the pyrrolinone scaffold (Scheme 6). Treatment of the lithium enolate derived from ketone (−)-**38** with pivalaldehyde furnished hydroxyketone (−)-**39**; Dess–Martin oxidation[28] then afforded dione (−)-**40** in 77% yield for the two steps. Pivalaldehyde was chosen both to mimic a sterically congested aldehyde, and for the initial study, to 'cap' the N-terminus of the developing pyrrolinone chain. Hydrogenation of dione **40** over Pd/C in MeOH resulted in the successive removal of the Cbz-protecting group, formation of the pyrrolinone ring by intramolecular condensation of the liberated amine, and deprotection of the primary alcohol to furnish monopyrrolinone (−)-**41**; the overall yield was 80%.[29]

Having achieved a viable method to construct the 2,5,5-substituted pyrrolinone ring system, we next explored the preparation of an aldehyde that would permit iterative extension of the polypyrrolinone chain. Unfortunately, all attempts to oxidize (−)-**41** to aldehyde **42** proved unsuccessful. Several oxidants were employed (e.g., TPAP,[18] PCC,[30] PDC,[31] Moffatt,[32] etc.); all resulted only in decomposition. This was even true of the Ireland–Swern protocol,[33] followed by low temperature addition of methyl magnesium bromide. Aldehyde **42** was simply too unstable to be prepared efficiently, presumably due to facile deformylation.[34] We therefore examined N-terminal extension of the pyrrolinone scaffold.

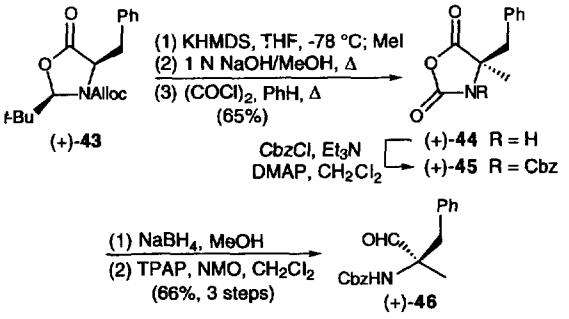


Scheme 6.

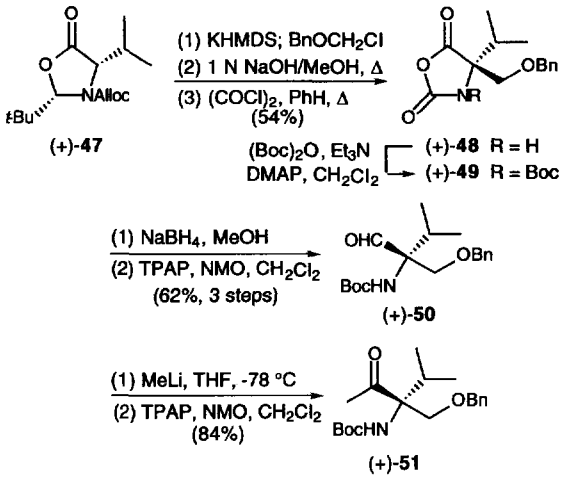
Preparation of monopyrrolinone (+)-**55**. Aldehyde (+)-**46** and ketone (+)-**51**, the starting materials required for the construction of monopyrrolinone (+)-**55**, were prepared by the same sequence employed to prepare **37** and **38**, beginning with D-phenylalanine and L-valine, respectively (Schemes 7 and 8).



Treatment of a 1:1 mixture of ketone (+)-**51** and aldehyde (+)-**46** with LiHMDS, followed by Dess–Martin oxidation[28] of the resulting alcohol, afforded dione (+)-**52** in 65% yield for the two steps (Scheme 9). Reductive removal of the Cbz-protecting group with concommitant closure of the pyrrolinone ring gave benzyl ether (+)-**53** in 88% yield. Hydrogenation with the more active Pearlman's catalyst[35] then provided alcohol (+)-**54**. Although the conversion of dione **52** to alcohol **54** could be accomplished in one step, isolation of benzyl ether **53** results in cleaner products and superior overall yields.

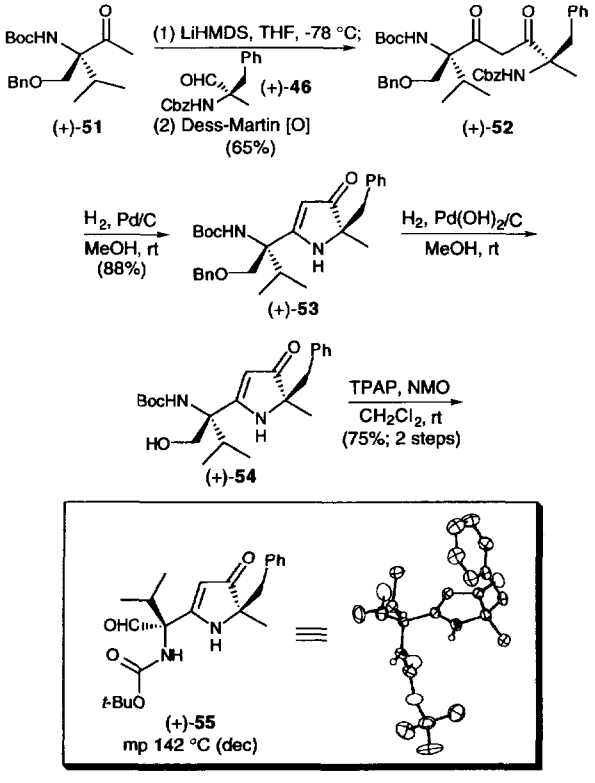


Scheme 7.



Scheme 8.

We were now faced with a formidable task: oxidation of alcohol (+)-**54** to aldehyde (+)-**55**, the latter a vinylog of aldehyde **42**. We reasoned, however, that the vinylogous displacement of the aldehyde carbonyl from the pyrrolinone ring, coupled with the fact that deformylation of **55** would not result in a pyrrole, would add some stability to the system. To our delight, alcohol (+)-**54** could be cleanly oxidized with TPAP/NMO[27] to furnish the desired aldehyde (+)-**55** in 75% overall yield from (+)-**53**. In fact, aldehyde (+)-**55** proved to be quite robust.[36] Recrystallization resulted in single crystals suitable for X-ray analysis; the ORTEP plot is shown in Scheme 9. As expected, the unit cell of



Scheme 9.

aldehyde (+)-**55**, like its 3,5,5-trisubstituted monopyrrolinone counterpart, showed no indication of β-sheet formation. A striking difference between the solid-state conformations of the two monopyrrolinone scaffolds was, however, revealed; the two side chains of the 3,5,5-trisubstituted pyrrolinones [e.g. (−)-**56** and (−)-**57**, Fig. 13] are oriented antiperiplanar, whereas the side chains of (+)-**55** are oriented coplanar. This result is readily explained by the intramolecular H-bond between the urethane N—H hydrogen and the enaminone carbonyl oxygen of pyrrolinones (−)-**56** and (−)-**57**, thereby forcing the antiperiplanar relationship of the side chains. An analogous hydrogen bond is not available in monopyrrolinone (+)-**55**.

Summary

To complement our 3,5-linked polypyrrolinone peptidomimetics, we have designed the related 2,5-linked polypyrrolinone scaffold. Molecular modeling comparisons of the two pyrrolinone motifs indicate that the 2,5-linked systems should display a greater tendency to exist in a linear strand conformation than their 3,5-linked counterparts and exhibit a different H-bonding pattern. Initial synthetic studies have led to an efficient protocol for construction of the 2,5,5-trisubstituted pyrrolinone ring system, containing the functionality required for N-terminal iterative extension. Efforts are currently underway to prepare carbonyl displaced polypyrrolinones utilizing this methodology, both to explore their conformational behavior and to exploit their potential as β-strand mimics; these results will be reported in due course.

Experimental

Materials and methods

All reactions were carried out under argon with dry, freshly distilled solvents, in vacuum-flamed glassware with magnetic stirring, except as otherwise indicated.

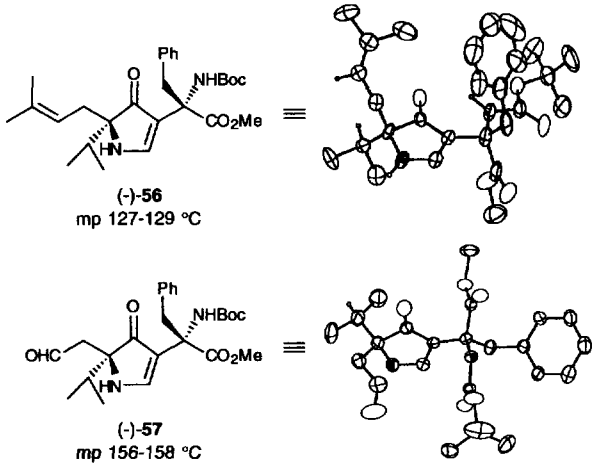


Figure 13. ORTEP plots for monopyrrolinones amides (−)-**56** and (−)-**57**.

Diethyl ether (Et_2O) and tetrahydrofuran (THF) and benzene, toluene and dichloromethane (CH_2Cl_2) were distilled from sodium/benzophenone, and calcium hydride, respectively. Triethylamine and pyridine were distilled from calcium hydride and stored over KOH.

All reactions were monitored by thin-layer chromatography (TLC) with 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, unless otherwise indicated.

All melting points were determined with a Thomas–Hoover apparatus and are corrected. IR spectra were recorded on a Perkin–Elmer Model 283B spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer and a Bruker WH-250 or WH-500 instrument, respectively. Chemical shifts are reported in δ values relative to tetramethylsilane. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Center with either a VG Micromass 70/70H or VG ZAB-E spectrometer. High performance liquid chromatography was performed with a Rainin 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. Normal-phase columns, 4.0, 10.0, or 25.0 mm × 25 cm with 8-μ (60 Å) packing, were purchased from Dynamax.

Microanalyses were performed by Robertson Labs, Madison, NJ.

Oxazolidinone (−)-30. To a cooled (−78 °C) soln of oxazolidinone (+)-**29** (10.0 g, 35 mmol) in THF (150 mL) was added KHMDS (0.5 M in toluene, 85 mL, 42 mmol) via a dropping funnel at a rate that sustained an internal temperature ≤ −70 °C. The resultant yellow soln was maintained at −78 °C for 20 min, at which time benzyloxymethyl chloride (12 mL, 88 mmol) was added. The resultant soln was maintained at −78 °C for 0.5 h, whereupon the reaction was quenched with 10% aq $NaHSO_4$ (300 mL) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were in turn washed with 10% aq $NaHSO_4$ (200 mL), satd aq $NaHCO_3$ (200 mL), and brine (200 mL), dried over $MgSO_4$, and concd. Purification of the residue by flash chromatography (5% EtOAc/hexanes) gave **30** (10.1 g, 72% yield) as a colorless oil: $[\alpha]_D^{20}$ −7.3° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3040 (s), 2980 (m), 1790 (m), 1720 (m), 1525 (m), 1430 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.31 (m, 2H), 7.30–7.27 (m, 1H), 7.21–7.20 (m, 2H), 5.88–5.82 (m, 1H), 5.64 (s, 1H), 5.29 (ddd, J = 17.2, 2.8, 1.4 Hz, 1H), 5.22 (ddd, J = 10.4, 2.2, 1.1 Hz, 1H), 4.62 (dd, J = 2.6, 1.2 Hz, 1H), 4.47 (ABq, J_{AB} = 12.1 Hz, $\Delta\nu$ = 79.2 Hz, 2H), 4.42–4.38 (m, 1H), 4.35–4.28 (m, 1H), 3.64 (d, J = 8.8 Hz, 1H), 2.10–2.05 (m, 1H), 1.81–1.76 (m, 2H), 1.02 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 155.3, 137.3, 131.7, 128.4 (2C), 127.5, 127.2 (2C), 118.7, 95.6, 72.9, 71.8, 69.7, 66.3, 42.6, 25.4 (3 C), 24.7, 24.3, 23.4; high resolution mass spectrum (CI, NH_3) *m/z* 421.2066 ($[M+NH_4]^+$; calcd for $C_{23}H_{37}N_2O_5$: 421.2072).

***N*-Carboxyanhydride (+)-35.** A soln of oxazolidinone (−)-**30** (10.0 g, 25 mmol) in a mixture of 1 N NaOH (110 mL) and MeOH (110 mL) was heated at reflux for 16 h, at which time the reaction was allowed to cool to room temperature and the MeOH removed in vacuo. The resultant mixture was diluted with H_2O (100 mL) and washed with Et_2O (2 × 50 mL). The aq phase was then acidified with 10% $NaHSO_4$ and then extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with H_2O (200 mL), and brine (200 mL), dried over $MgSO_4$, and concd in vacuo.

A soln of the crude residue in benzene (75 mL) was treated with oxalyl chloride (4.3 mL, 50 mmol) and the resultant soln heated at reflux for 20 min. The reaction was then allowed to cool to room temperature and was concd in vacuo to furnish **35**, which was used without further purification. An analytical sample was purified by flash chromatography (20% EtOAc/hexanes): mp 72–74 °C; $[\alpha]_D^{20}$ +34.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3420 (w), 3030 (s), 2975 (m), 1850 (m), 1790 (s), 1520 (m), 1420 (m), 1215 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H), 6.66 (br s, 1H), 4.51 (ABq, J_{AB} = 12.3 Hz, $\Delta\nu$ = 16.2 Hz, 2H), 3.55 (ABq, J_{AB} = 9.7 Hz, $\Delta\nu$ = 81.4 Hz, 2H), 1.77–1.73 (m, 1H), 1.70–1.61 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 152.8, 136.6, 128.5 (2C), 128.0, 127.5 (2C), 73.4, 72.4, 67.5, 40.5, 24.1, 23.8, 22.5; high resolution mass spectrum (CI, NH_3) *m/z* 295.1665 ($[M+NH_4]^+$; calcd for $C_{15}H_{23}N_2O_4$: 295.1658).

Aldehyde (−)-37. To a cooled (0 °C) soln of the crude anhydride (+)-**35** (6.9 g, 25 mmol) in CH_2Cl_2 (300 mL) was added sequentially Et_3N (17 mL, 120 mmol), DMAP (310 mg, 2.5 mmol), and benzyl chloroformate (4.3 mL, 30 mmol). The resultant soln was maintained at 0 °C for 1 h, at which time the reaction was diluted with Et_2O (500 mL) and washed with 10% aq $NaHSO_4$ (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$, and concd in vacuo.

A cooled (0 °C) soln of the crude residue in MeOH (250 mL) was treated with $NaBH_4$ (4.5 g, 120 mmol) and the resultant soln maintained at 0 °C for 1 h. The reaction was then quenched with 10% aq $NaHSO_4$ (250 mL) and the resultant mixture stirred at room temperature for 4 h. The MeOH was then removed in vacuo and the residue diluted with H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were then washed with 10% aq $NaHSO_4$ (150 mL) and brine (150 mL), dried over $MgSO_4$, and concd in vacuo.

To a soln of the crude primary alcohol in CH_2Cl_2 (250 mL) was added powdered molecular sieves (4 Å, 5 g), followed by NMO (4.4 g, 38 mmol) and TPAP (440 mg, 1.3 mmol). The resultant mixture was stirred at room temperature for 1 h, at which time the reaction was concd in vacuo. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded aldehyde **37** (5.5 g, 59% yield from **30**) as a colorless oil: $[\alpha]_D^{20} - 10.2°$ (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3020 (m), 2970 (m), 1720 (s), 1510 (s), 1230 (m), 1100 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.37–7.28 (m, 8H), 5.88 (br s, 1H), 5.11 (s, 2H), 4.51 (d, $J = 12.1$ Hz, 1H), 4.43 (d, $J = 12.1$ Hz, 1H), 3.87 (ABq, $J_{AB} = 9.7$ Hz, $\Delta\nu = 134.3$ Hz, 2H), 2.18–2.16 (m, 2H), 1.65–1.60 (m, 1H), 0.91 (d, $J = 5.6$ Hz, 3H), 0.80 (d, $J = 5.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.3, 154.6, 137.4, 136.3, 128.3 (2C), 128.2 (2C), 127.9, 127.7, 127.6, 127.4 (2C), 73.3, 69.7, 66.6, 66.3, 38.1, 23.8, 23.5, 23.2; high resolution mass spectrum (CI, NH_3) *m/z* 370.2011 ($[M+H]^+$; calcd for $C_{22}H_{28}NO_4$: 370.2018). Anal. calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.53; H, 7.28; N, 3.79.

Ketone (−)-38. To a cooled (−78 °C) soln of aldehyde (−)-**37** (3.4g, 9.2 mmol) in THF (100 mL) was added MeLi (1.4 M in Et_2O, 20 mL, 28 mmol). The resultant soln was maintained at −78 °C for 1 h, at which time the reaction was quenched with 10% aq $NaHSO_4$ (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, and concd in vacuo.

A soln of the crude residue was dissolved in CH_2Cl_2 (100 mL) and treated sequentially with powdered molecular sieves (4 Å, 2 g), NMO (1.6 g, 14 mmol), and TPAP (160 mg, 0.46 mmol). The resultant mixture was stirred at room temperature for 1 h, at which time the reaction was concd in vacuo. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded ketone **38** (2.8 g, 80% yield from **37**) as a colorless solid: mp 56–57 °C; $[\alpha]_D^{20} - 2.1°$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3405 (m), 3020 (m), 2960 (m), 1715 (s), 1500 (s), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (m, 8H), 7.26–7.21 (m, 2H), 6.31 (br s, 1H), 5.09 (s, 2H), 4.54 (d, $J = 12.1$ Hz, 1H), 4.38 (d, $J = 12.1$ Hz, 1H), 3.93 (ABq, $J_{AB} = 10.0$ Hz, $\Delta\nu = 263.4$ Hz, 2H), 2.32–2.27 (m, 1H), 2.17 (s, 3H), 1.57–1.52 (m, 2H), 0.87 (d, $J = 6.3$ Hz, 3H), 0.78 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.2, 154.2, 137.5, 136.6, 128.3 (2C), 128.2 (2C), 127.8, 127.7, 127.6 (2C), 127.5 (2C), 73.3, 70.9, 68.3, 66.0, 38.9, 23.9, 23.8, 23.5, 23.1; high resolution mass spectrum (CI, NH_3) *m/z* 384.2165 ($[M+H]^+$; calcd for $C_{23}H_{30}NO_4$: 384.2174). Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.70; H, 7.47; N, 3.25.

Dione (−)-40. To a cooled (−78 °C) soln of ketone (−)-**38** (2.5 g, 6.5 mmol) in THF (50 mL) was added LiHMDS (1.0 M in THF, 16 mL, 16 mmol). The resultant soln was maintained at −78 C for 0.5 h, at which time pivalaldehyde (1.4 mL, 13 mmol) was added. The resultant soln was maintained at −78 °C for 0.5 h, whereupon the reaction was quenched with satd aq NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and concd in vacuo.

A soln of the crude residue in CH_2Cl_2 (100 mL) was treated with pyridine (2.5 mL, 33 mmol), followed by the Dess–Martin periodinane (2.8 g, 6.5 mmol). The resultant soln was maintained at room temperature for 1 h, at which time the reaction was diluted with Et_2O (200 mL) and washed with 20% aq $Na_2S_2O_3$ (2 × 100 mL), satd aq $NaHCO_3$ (2 × 100 mL), and brine (100 mL), dried over $MgSO_4$, and concd in vacuo. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded dione **40** (2.4 g, 77% yield from **38**) as a colorless oil: $[\alpha]_D^{20} - 3.2°$ (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3400 (w), 3030 (w), 2980 (m), 1720 (m), 1595 (m), 1495 (m), 1425 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 8H), 7.23–7.21 (m, 2H), 6.37 (br s, 1H), 5.72 (s, 1H), 5.09 (s, 2H), 4.56 (d, $J = 12.4$ Hz, 1H), 4.37 (d, $J = 12.4$ Hz, 1H), 4.10 (br d, $J = 9.5$ Hz, 1H), 3.62 (d, $J = 9.5$ Hz, 1H), 2.30–2.27 (m, 1H), 1.60–1.49 (m, 2H), 1.17 (s, 9H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.74 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 192.4, 154.3, 137.8, 136.8, 128.4, 128.3 (2C), 128.2 (2C), 127.8, 127.7, 127.5, 127.4 (2C), 91.1, 73.2, 71.1, 66.0, 65.7, 40.3, 37.4, 27.4 (3C), 25.7, 23.8, 23.3; high resolution mass spectrum (CI, NH3) *m/z* 468.2771 ($[M+H]^+$; calcd for $C_{28}H_{38}NO_5$: 468.2750). Anal. calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00. Found: C, 71.75; H, 8.24; N, 2.77.

Monopyrrolinone (−)-41. A mixture of dione (−)-**40** (1.8 g, 3.9 mmol) and 5% Pd/C (360 mg, 20 wt%) in MeOH (80 mL) was evacuated in vacuo and refilled with H_2 several times. The resultant mixture was vigorously stirred at room temperature under 1 atm of H_2 (maintained with a balloon) for 16 h, whereupon the reaction was filtered through Celite and concd in vacuo. Purification of the residue by flash chromatography (2% MeOH/$CHCl_3$) furnished monopyrrolinone **41** (700 mg, 80% yield) as a sticky-yellow oil: $[\alpha]_D^{20} - 12.2°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3320 (w, br), 3035 (s), 2980 (m), 1695 (m), 1540 (m), 1480 (m), 1430 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (br s, 1H), 5.01 (d, $J = 1.6$ Hz, 1H), 4.42 (br s, 1H), 3.47 (s, 2H), 1.85 (dd, $J = 14.2$, 6.0 Hz, 1H), 1.69 (dd, $J = 14.2$, 6.6 Hz, 1H), 1.56–1.50 (m, 1H), 1.23 (s, 9H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 189.4, 95.6, 72.9, 67.8, 40.4, 33.7, 28.3 (3 C), 24.3, 24.1, 23.9; high resolution mass spectrum (CI, NH_3) *m/z* 226.1805 ($[M+H]^+$; calcd for $C_{13}H_{24}NO_2$: 226.1807).

***N*-Carboxyanhydride (+)-44.** To a cooled (−78 °C) soln of oxazolidinone (+)-**43** (9.2 g, 29 mmol) in THF (150 mL) was added KHMDS (0.5 M in toluene, 120 mL, 58 mmol) via a dropping funnel at a rate that sustained an internal temperature of −70 °C. The resultant yellow soln was maintained at −78 °C for 20 min, at which time methyl iodide (18 mL, 290 mmol)

was added. The resultant soln was maintained at ≤ -78 °C for 0.5 h, whereupon the reaction was allowed to warm to room temperature. The reaction was then quenched with 10% aq $NaHSO_4$ (150 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with 10% aq $NaHSO_4$ (200 mL), satd aq $NaHCO_3$ (200 mL), and brine (200 mL), dried over $MgSO_4$, and concd to provide the alkylated oxazolidinone as a colorless oil, which was used without further purification. An analytical sample was purified by flash chromatography (5% EtOAc/hexane): $[\alpha]_D^{20}$ −61.6° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3025 (s), 2980 (m), 1795 (m), 1715 (m), 1525 (m), 1425 (m), 1215 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H), 5.99–5.91 (m, 1H), 5.47 (s, 1H), 5.39 (dd, J = 17.2, 1.2 Hz, 1H), 5.31 (dd, J = 10.4, 1.1 Hz, 1H), 4.71–4.67 (m, 1H), 4.65–4.61 (m, 1H), 3.32 (ABq, J_{AB} = 13.8 Hz, Δν = 38.3 Hz, 2H), 1.59 (s, 3H), 0.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 155.4, 135.8, 131.5, 130.8 (2C), 128.1 (2C), 127.1, 119.4, 94.2, 66.6, 64.7, 42.3, 37.4, 24.7; high resolution mass spectrum (CI, NH_3) *m/z* 349.2123 ($[M+NH_4]^+$; calcd for $C_{19}H_{29}N_2O_4$: 349.2127). Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.89; H, 7.66; N, 4.19.

Following the procedure decribed above for (+)-**35**, the crude alkylated oxazolidinone was hydrolyzed with 1 N NaOH (140 mL) and MeOH (140 mL); reaction of the resultant acid with oxalyl chloride (5 mL, 58 mmol) furnished the crude anhydride **44**. Purification of the residue by flash chromatography (30%→50% EtOAc/hexanes) gave anhydride **44** (3.8 g, 65% yield from **43**) as a waxy solid: mp 79–81 °C; $[\alpha]_D^{20}$ +49.9° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3425 (w), 3030 (s), 2980 (m), 1855 (m), 1795 (s), 1525 (m), 1425 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.30 (m, 3H), 7.16–7.13 (m, 2H), 6.72 (br s, 1H), 3.06 (ABq, J_{AB} = 13.9 Hz, Δν = 97.6 Hz, 2H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 151.8, 132.9, 129.9 (2C), 128.8 (2C), 127.9, 43.8, 26.1, 23.6; high resolution mass spectrum (CI, NH_3) *m/z* 223.1076 ($[M+NH_4]^+$; calcd for $C_{11}H_{15}N_2O_3$: 223.1083).

Aldehyde (+)-46. Following the procedure decribed above for (−)-**37**, anhydride (+)-**44** (2.0 g, 9.7 mmol) was reacted with Et_3N (6.8 mL, 49 mmol), DMAP (120 mg, 0.97 mmol), and benzyl chloroformate (1.7 mL, 12 mmol) to furnish (+)-**45**. Reduction with $NaBH_4$ (1.8 g, 49 mmol), oxidation of the resultant primary alcohol with TPAP (170 mg, 0.49 mmol) and NMO (1.7 g, 15 mmol), and purification by flash chromatography (20% EtOAc/hexanes) afforded aldehyde **46** (1.9 g, 66% yield from **44**) as a colorless solid: mp 69–70 °C; $[\alpha]_D^{20}$ +13.0° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3430 (w), 3405 (w), 3020 (m), 1740 (m), 1720 (s), 1505 (s), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.41–7.35 (m, 6H), 7.27–7.24 (m, 2H), 7.04–7.01 (m, 2H), 5.28 (br s, 1H), 5.15 (s, 2H), 3.17 (ABq, J_{AB} = 13.8 Hz, Δν = 19.1 Hz, 2H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 155.0, 136.1, 135.0, 130.0 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 128.0, 126.8, 66.6, 62.7, 39.0, 19.8; high resolution mass spectrum (CI, NH_3) *m/z* 298.1448 ($[M+H]^+$; calcd for $C_{18}H_{20}NO_3$: 298.1443).

***N*-Carboxyanhydride (+)-48**. Following the procedure described above for (+)-**35**, reaction of oxazolidinone (+)-**47** (7.0 g, 26 mmol), KHMDS (0.5 M in toluene, 62 mL, 31 mmol), and benzyloxymethyl chloride (9.0 mL, 65 mmol), followed by work up and flash chromatography (5% EtOAc/hexanes), provided the alkylated oxazolidinone (7.0 g, 70% yield) as a colorless oil: $[\alpha]_D^{20}$ −3.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3030 (s), 2985 (m), 1785 (m), 1715 (m), 1525 (m), 1425 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.29–7.27 (m, 2H), 7.24–7.22 (m, 2H), 5.88–5.80 (m, 1H), 5.62 (s, 1H), 5.27 (dd, J = 17.2, 1.4 Hz, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H), 4.45 (dd, J = 12.9, 5.9 Hz, 1H), 4.46 (ABq, J_{AB} = 12.1 Hz, Δν = 26.6 Hz, 2H), 4.43–4.41 (m, 1H), 4.24 (d, J = 8.7 Hz, 1H), 3.82 (d, J = 8.7 Hz, 1H), 2.30 (app hep, J = 7.0 Hz, 1H), 1.16–1.13 (m, 6H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 155.6, 137.4, 131.8, 128.2 (2C), 127.5, 127.1 (2C), 118.7, 95.5, 73.0, 69.8, 68.4, 66.4, 37.3, 33.7, 25.6, 18.6, 17.8; high resolution mass spectrum (CI, NH_3) *m/z* 407.2540 ($[M+NH_4]^+$; calcd for $C_{22}H_{35}N_2O_5$: 407.2546).

The alkylated oxazolidinone (7.0 g, 18 mmol) was hydrolyzed with 1 N NaOH (70 mL) and MeOH (70 mL); reaction of the resultant crude acid with oxalyl chloride (1.6 mL, 36 mmol) furnished crude anhydride **48**. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded anhydride **48** (3.6 g, 76% yield) as a beige solid: mp 122–124 °C; $[\alpha]_D^{20}$ +11.7° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3030 (s), 2980 (m), 1855 (m), 1785 (s), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H), 6.98 (br s, 1H), 4.52 (s, 2H), 3.67 (ABq, J_{AB} = 9.7 Hz, Δν = 44.4 Hz, 2H), 2.16–2.11 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 153.4, 136.7, 128.4 (2C), 127.9, 127.4 (2C), 73.4, 71.6, 70.7, 31.5, 16.8, 16.5; high resolution mass spectrum (CI, NH3) *m/z* 281.1508 ($[M+NH_4]^+$; calcd for $C_{14}H_{21}N_2O_4$: 281.1501). Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.21; H, 6.59; N, 5.35.

Aldehyde (+)-50. Following the procedure described above for (−)-**37**, anhydride (+)-**48** (2.5 g, 9.5 mmol) was reacted with Et_3N (6.6 mL, 48 mmol), DMAP (120 mg, 0.95 mmol), and di-*tert*-butyl dicarbonate (2.5 g, 12 mmol) to provide (+)-**49**. Reduction with $NaBH_4$ (1.8 g, 48 mmol), oxidation of the resultant primary alcohol with TPAP (160 mg, 0.5 mmol) and NMO (1.6 g, 14 mmol) and purification by flash chromatography (10% EtOAc/hexanes) afforded aldehyde **50** (1.9 g, 62% yield from **48**) as a colorless oil: $[\alpha]_D^{20}$ +21.6° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3425 (w), 3030 (s), 2980 (m), 1735 (m), 1715 (m), 1500 (m), 1425 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.37–7.32 (m, 2H), 7.29–7.25 (m, 3H), 5.25 (br s, 1H), 4.51 (ABq,

J_{AB} = 12.1 Hz, $\Delta\nu$ = 23.8 Hz, 2H), 4.08–4.02 (m, 1H), 3.89–3.84 (m, 1H), 2.37–2.31 (m, 1H), 1.44 (s, 9H), 1.00 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 155.1, 137.8, 128.3 (2C), 127.6, 127.5 (2C), 73.5, 68.7, 67.9, 67.7, 30.8, 28.2 (3C), 17.1, 17.0; high resolution mass spectrum (CI, NH_3) m/z 322.2007 ($[M+H]^+$; calcd for $C_{18}H_{28}NO_4$: 322.2018).

Ketone (+)-**51**. Following the procedure decribed above for (−)-**38**, aldehyde (+)-**50** (1.7 g, 5.3 mmol) was reacted with MeLi (1.4 M in Et_2O, 11 mL, 16 mmol). Oxidation of the resultant alcohol with TPAP (93 mg, 0.3 mmol) and NMO (930 mg, 8.0 mmol) and purification by flash chromatography (10% EtOAc/hexanes) gave ketone **51** (1.5 g, 84% yield) as a colorless oil: $[\alpha]_D^{20}$ +33° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3400 (w), 3020 (s), 2980 (m), 1720 (s), 1495 (s), 1215 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 7.28–7.25 (m, 3H), 5.56 (br s, 1H), 4.51 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu$ = 49.6 Hz, 2H), 4.39 (br d, J = 8.6 Hz, 1H), 3.85–3.82 (m, 1H), 2.21–2.17 (m, 1H), 2.16 (s, 3H), 1.43 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.0, 155.0, 138.0, 128.2 (2C), 127.9, 127.5 (2C), 79.1, 73.3, 70.1, 68.5, 31.9, 28.2 (3C), 25.4, 17.8, 17.3; high resolution mass spectrum (CI, NH_3) m/z 336.2169 ($[M+H]^+$; calcd for $C_{19}H_{30}NO_4$: 336.2174).

Dione (+)-**52**. To a cooled (−78 °C) soln of aldehyde (+)-**46** (500 mg, 1.7 mmol) and ketone (+)-**51** (590 mg, 1.8 mmol) in THF (20 mL) was added LiHMDS (1.0 M in THF, 8.4 mL, 8.4 mmol). The resultant soln was maintained at −78 °C for 0.5 h, at which time the reaction was quenched with satd aq NH_4Cl (20 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concd in vacuo.

Following the procedure decribed above for dione (−)-**40**, oxidation of the crude residue with the Dess–Martin periodinane (710 mg, 1.7 mmol) and pyridine (0.7 mL, 8.4 mmol), followed by work up and flash chromatography (20% EtOAc/hexanes), provided dione **52** (690 mg, 65% yield) as a yellow oil: $[\alpha]_D^{20}$ +43.5° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3410 (w), 3035 (s), 2980 (m), 1725 (m, br), 1505 (m), 1220 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.26 (m, 10H), 7.23–7.18 (m, 3H), 7.02–7.00 (m, 2H), 5.30 (br s, 1H), 5.22 (br s, 1H), 5.11 (s, 2H), 4.49 (ABq, J_{AB} = 12.1 Hz, $\Delta\nu$ = 10.3 Hz, 2H), 4.06 (d, J = 9.7 Hz, 1H), 3.97 (d, J = 9.7 Hz, 1H), 3.45 (d, J = 11.8 Hz, 1H), 3.22 (d, J = 11.8 Hz, 1H), 2.68–2.62 (m, 1H), 1.55–1.42 (m, 5H), 1.41 (s, 9H), 0.99 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 197.7, 155.4, 154.8, 137.4, 136.2, 135.1, 130.4 (2C), 128.5 (2C), 128.4, 128.3 (2C), 128.2 (2C), 128.1, 128.0, 127.7, 127.5 (2C), 126.8, 80.3, 74.0, 73.4, 68.5, 66.7, 63.2, 40.3, 31.0, 28.2 (3C), 28.1, 21.9, 17.3, 17.1; high resolution mass spectrum (CI, NH_3) m/z 631.3401 ($[M+H]^+$; calcd for $C_{37}H_{47}N_2O_7$: 631.3383).

Monopyrrolinone (+)-**53**. A mixture of dione (+)-**52** (450 mg, 0.7 mmol) and 5% Pd/C (90 mg, 20 wt%) in MeOH (50 mL) was evacuated in vacuo and refilled with H_2 several times. The resultant mixture was stirred vigorously at room temperature under 1 atm of H_2 (maintained with a balloon) for 6 h, whereupon the reaction was filtered through Celite and concd in vacuo. Purification of the residue by flash chromatography (20→50% EtOAc/hexanes) furnished monopyrrolinone **53** (300 mg, 88% yield) as a colorless solid: mp 58–60 °C; $[\alpha]_D^{20}$ +92.7° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3420 (w), 3035 (s), 2980 (m), 1720 (m), 1655 (m), 1530 (m), 1480 (m), 1425 (m), 1220 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.24 (m, 5H), 7.21–7.14 (m, 5H), 6.42 (br s, 1H), 4.96 (br s, 1H), 4.93 (d, J = 1.2 Hz, 1H), 4.50 (ABq, J_{AB} = 11.7 Hz, $\Delta\nu$ = 35.0 Hz, 2H), 3.77 (ABq, J_{AB} = 9.5 Hz, $\Delta\nu$ = 54.2 Hz, 2H), 2.86 (ABq, J_{AB} = 13.5 Hz, $\Delta\nu$ = 101.2 Hz, 2H), 2.46–2.43 (m, 1H), 1.40 (s, 9H), 1.22 (s, 3H), 0.80 (d, J = 6.9 Hz, 3H), 0.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 179.1, 155.3, 137.0, 136.3, 129.9 (2C), 128.3 (2C), 127.9 (2C), 127.8, 127.6 (2C), 126.4, 97.1, 80.2, 73.5, 69.2, 67.3, 61.0, 42.8, 31.4, 28.0 (3C), 22.0, 16.7, 16.4; high resolution mass spectrum (CI, NH_3) m/z 479.2886 ($[M+H]^+$; calcd for $C_{29}H_{39}N_2O_4$: 479.2909). Anal. calcd for $C_{29}H_{38}NO_4$: C, 72.77; H, 8.00; N, 5.85. Found: C, 73.00; H, 8.34; N, 5.60.

Monopyrrolinone aldehyde (+)-**55**. A mixture of monopyrrolinone (+)-**53** (1.1 g, 2.3 mmol) and 20% $Pd(OH)_2$/C (110 mg, 10 wt%) in MeOH (100 mL) was evacuated in vacuo and refilled with H_2 several times. The resultant mixture was stirred vigorously at room temperature under 1 atm of H_2 (maintained with a balloon) for 24 h, whereupon the reaction was filtered through Celite and concd in vacuo. An analytical sample was purified by flash chromatography (2% MeOH/$CHCl_3$): mp 117 °C (dec); $[\alpha]_D^{20}$ +77.9° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3430 (w, br), 3040 (s), 2980 (m), 1715 (m), 1660 (m), 1525 (m), 1480 (m), 1425 (m), 1280 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7.14 (m, 5H), 6.98 (br s, 1H), 5.25 (br s, 1H), 5.08 (s, 1H), 4.32 (br s, 1H), 3.93–3.85 (m, 2H), 2.89 (ABq, J_{AB} = 11.5 Hz, $\Delta\nu$ = 62.4 Hz, 2H), 2.34–2.26 (m, 1H), 1.42 (s, 9H), 1.25 (s, 3H), 0.84 (br s, 3H), 0.67 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 180.9, 156.7, 135.8, 130.0 (2C), 128.0 (2C), 126.6, 97.2, 80.7, 68.1, 63.4, 62.5, 42.8, 33.3, 28.1 (3C), 21.9, 16.8, 16.4; high resolution mass spectrum (CI, NH_3) m/z 389.2427 ($[M+H]^+$; calcd for $C_{22}H_{33}N_2O_4$: 389.2440).

To a soln of the crude alcohol in CH_2Cl_2 (25 mL) was added sequentially powdered molecular sieves (4 Å, 500 mg), NMO (410 mg, 3.5 mmol), and TPAP (81 mg, 0.23 mmol). The resultant mixture was stirred at room temperature for 1 h, at which time the reaction was filtered through a silica gel plug and eluted first with CH_2Cl_2 (50 mL), followed by 50% EtOAc/hexanes (75 mL). The EtOAc/hexanes eluent was dried over $MgSO_4$ and concd in vacuo to furnish monopyrrolinone aldehyde **55** (670 mg, 75% yield) as a slightly yellow solid: mp 142 °C (dec); $[\alpha]_D^{20}$ +24.5° (*c* 1.5, $CHCl_3$); IR

($CHCl_3$) 3420 (w, br), 3040 (s), 2980 (m), 1715 (m), 1660 (m), 1525 (m), 1480 (m), 1425 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.32–7.23 (m, 3H), 7.21–7.17 (m, 2H), 6.79 (br s, 1H), 5.26 (br s, 1H), 5.02 (s, 1H), 2.85–2.79 (m, 2H), 2.32–2.26 (m, 1H), 1.44 (s, 9H), 1.21 (s, 3H), 0.94–0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 240.1, 198.9, 175.3, 155.9, 136.0, 130.2 (2C), 128.3 (2C), 126.8, 96.8, 81.7, 67.8, 66.2, 42.9, 34.9, 28.1 (3C), 21.1, 16.9, 16.5; high resolution mass spectrum (CI, NH_3) *m/z* 387.2298 ($[M+H]^+$; calcd for $C_{22}H_{31}N_2O_4$: 387.2283).

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