Total Syntheses of (±)- and (−)-Stemoamide

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Abstract: (±)-Stemoamide (**1**) was prepared in seven steps beginning with γ-chlorobutryl chloride (**20**) and succinimide (**15**), which were efficiently converted to the key alkyne oxazole **17** on a multigram scale. Intramolecular (Diels−Alder)−(*retro*-Diels−Alder) reaction of **17** then gave butenolide **12b** directly upon aqueous workup. The remaining two stereocenters in **1** were established in a single step by a highly selective reduction of **12b** ($NaBH_4/NiCl_2$), followed by equilibration to the thermodynamically favored natural configuration. In analogous fashion (−)-stemoamide (**1**) was prepared beginning with L-pyroglutamic acid (*S*-**35**).

Introduction

Stemoamide (**1**) is a member of the *stemona* class of alkaloids that was isolated in 1992 from *Stemona tuberosa*, and whose structure was elucidated by an extensive series of 2D NMR experiments together with IR spectroscopy (Figure 1).[1a] Extracts

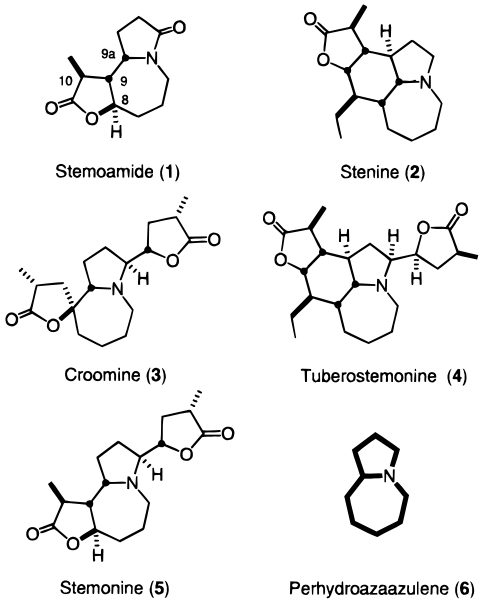

Figure 1. Stemona alkaloids.

of the *Stemona* species (and the closely related *Croomiacea*) have been employed in Chinese traditional medicine for many years, both in managing certain respiratory disorders (bronchitis, pertussis, and tuberculosis) and also as anthelmintics (i.e., antiparasitic agents).[2] However, it is only relatively recently that a number of pure constituents have been isolated and characterized, utilizing X-ray crystallography in combination with degradation studies and spectroscopy.[3] In addition to **1**, members of the *stemona* class include stenine (**2**), croomine (**3**), tuberostemonine (**4**), and stemonine (**5**). A distinguishing feature of this group is the presence of a perhydroazaazulene ring (cf. **6**), and most members also contain an α-methyl-γ-butryolactone functionality.

Not surprisingly, members of this class have attracted considerable attention, and several partial and total syntheses have appeared in the past few years. These include syntheses of (±)-stenine (1990)[4a] and (−)-stenine (1995),[4b] (+)-croomine (1989, 1996),[4c,d] and the tricyclic core of tuberostemonine (1996).[4e] In addition, four syntheses of stemoamide (**1**) have been reported,[4f−i] making this compound the most sought after target of the group. The first of these was carried out by Williams et al. (1994),[4f] who prepared (−)-**1** in ∼25 steps beginning with (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate. Subsequently, Narasaka et al. reported a synthesis of (±)-**1** featuring sequential oxidative couplings of appropriately substituted organostannanes with ketone silyl enol ethers (1996).[4g] Also in 1996, Mori et al. described a novel synthesis of (−)-**1**

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(1) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

(2) For leading references, see: (a) Goetz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1976; Vol. IX, pp 545−551. (b) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. In *Natural Products Chemistry*; Academic Press: New York, 1975; Vol. 2, pp 292−93. See also ref 1.

(3) For leading references see: (a) Ye, Y.; Qin, G.; Xu, R.-S. *Phytochemistry* **1994**, *37*, 1201, 1205. (b) Cheng, D.; Guo, J.; Chu, T. T.; Röder, E. *J. Nat. Prod.* **1988**, 51, 202. (c) Xu, R.-S.; Lu, Y.-J.; Chu, J.-H.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667. See also ref 1.

(4) (a) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (d) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. (e) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739. (f) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417 (g) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063. (h) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. Kinoshita, A.; Mori, M. *J. Org. Chem. Heterocycles* **1997**, *46* 287. See also: Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1. (i) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. Related synthetic efforts: (j) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773. (k) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55. (l) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538. (m) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (n) Xiang, L. I.; Kozikowski, A. P. *Synlett* **1990**, *2*, 279. (o) Unless otherwise indicated all structures refer to racemic compounds.

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utilizing a Ru-catalyzed enyne metathesis reaction.[4h] In this paper we provide experimental details for a conceptually new synthesis of (±)-stemoamide, which affords (±)-**1** in seven steps beginning with γ-chlorobutryl chloride.[4i] In addition, we describe a concise synthesis of enantiomerically pure (−)-stemoamide (**1**).

Background

Our synthetic plan took advantage of the exceptional reactivity of alkyne oxazoles **7** in intramolecular Diels−Alder cyclizations (Figure 2).[5a] Transformations of this type lead directly to highly

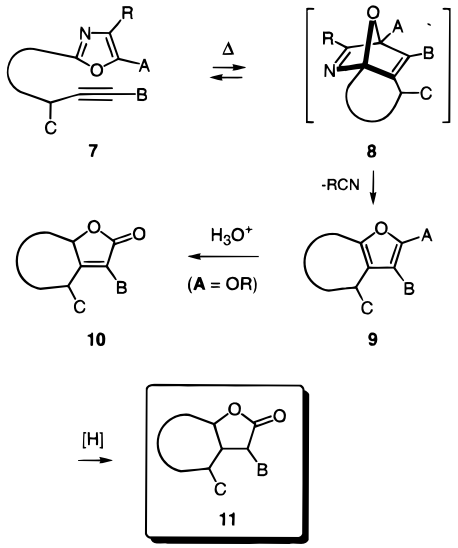


Figure 2. Synthetic strategy.

substituted furans **9**, via intermediate adducts **8** that suffer rapid loss of RCN. When **A** = alkoxy, mild acid hydrolysis of **9** affords butenolides **10**, a conversion that we have previously employed in syntheses of paniculide A and norsecurinine.[5b,c] Finally, reduction of **10** provides a versatile route to lactones **11**.[5a] This approach seemed well suited for constructing the carbon skeleton of **1**.

A potentially more difficult task pertained to stereochemical control at C_8−C_{10}, but here nature greatly simplified our task (Figure 3). Inspection of models indicates that each of the

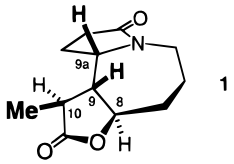


Figure 3. Energy minimum.

stereogenic centers in **1** is in the thermodynamically most favored configuration (i.e., **1** is the most stable of eight possible diastereomers). In principle, then, equilibration at each of these centers should lead ultimately to the "natural" relative stereochemistry, an iteration that is readily achieved computationally. Experimentally, such a "global" minimization is not possible, since only C_{10} in **1** represents an epimerizable site. In practice, however, the same result would obtain were each of these operations carried out sequentially, so long as the stereogenic centers were introduced in proper order. One strategy for realizing this goal is outlined below.

We first addressed the issue of stereochemical control at the noncontiguous C_8 and C_{9a} stereocenters. In stemoamide (**1**) these centers are not epimerizable, and they are too far apart for effective control by asymmetric induction (cf. Figure 3). However, this situation changes markedly upon introduction of a double bond at C_9−C_{10} (Figure 4). Now *both* C_8 and C_{9a} are

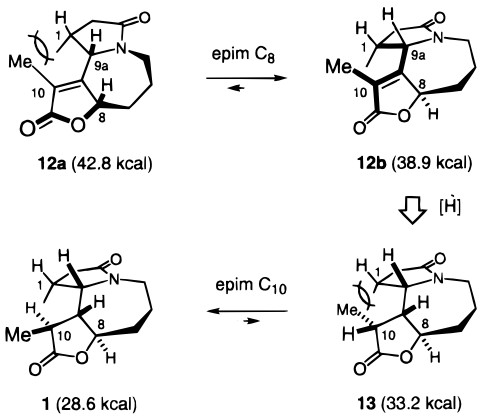


Figure 4. Sequential epimerization.

epimerizable, and they are able to directly interact with each other. On this basis we chose butenolide **12b** as the key intermediate for establishing the trans relative stereochemistry of **1** at C_8 and C_{9a} under thermodynamic control. Models show that the isomeric *cis*-butenolide **12a** suffers from severe steric crowding. Mainly this is due to the fact that the C_{10} methyl group is forced into close proximity to the C_1 methylene hydrogens. In this arrangement, the C_{10} methyl bond and the C_1−C_{9a} pyrrolidinone bond have a dihedral angle close to 0° (pseudoeclipsed). Assuming free equilibration, epimerization at C_8 in **12a** has the effect of increasing this dihedral angle to ∼60° (pseudostaggered), thereby greatly reducing steric interactions. This relationship, which is qualitatively apparent with models, was quantified with molecular mechanics calculations (MM2*), which gave $\Delta H_{a,b} = 3.9$ kcal/mol for the strain energy difference between **12a** and **12b**.[6] Epimerization at C_{9a} in **12a**, while having the same effect, was viewed as less likely due to the lower pK_a of H_8 (the validity of this assumption was later demonstrated with enantiomerically pure (−)-**12b**, vide infra). Once in hand, cis reduction of **12b** from the least hindered β-face would afford the methyl lactone **13**, which again suffers from van der Waal's repulsion between Me_{10} and C_1. However, inversion at the now epimerizable C_{10}-position would relieve this interaction, and produce stemoamide (**1**) as the thermodynamically most stable product (MM2* $\Delta H_{13,1} = 4.6$ kcal/mol).[6]

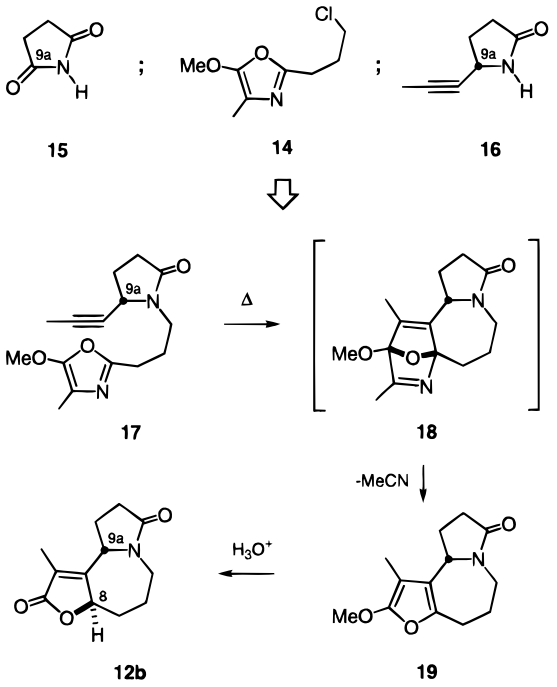
Discussion and Results

(±)-Stemoamide (1). Our initial goal was the synthesis of the alkyne oxazole **17**, which we believed to be only two steps removed from the key butenolide **12b** (Scheme 1).[4o] These steps involved thermolysis of **17** to afford the methoxyfuran **19**, followed by mild acid hydrolysis.[5] It was uncertain whether **12b** might be produced directly from **19** via a kinetically controlled

(5) (a) Jacobi, P. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; Jai Press Inc.: Greenwich, CT, 1992; Vol. II, pp 251−98 and references therein. (b) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. S. *Tetrahedron* **1987**, *43*, 5475. (c) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384.

(6) (a) Calculations were carried out using MacroModel V5.5, employing the MM2* force field, and using Monte Carlo simulations to locate global minima (>1000 MC steps).[6b] (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. See also: (c) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

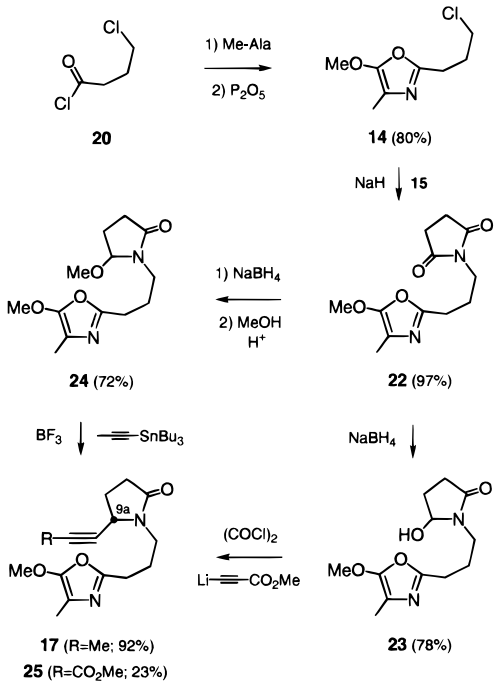
Scheme 1



pathway (i.e. initial protonation at the α-face). However, we were confident that the desired 8α-stereochemistry would be favored under equilibrating conditions (cf. Figure 4). An attractive feature of this approach was the simplicity of the alkyne oxazole **17**, which we planned to synthesize by coupling of the 2-(3-chloropropyl) oxazole **14** with a suitable amine nucleophile. Potential coupling partners included succinimide (**15**) and the alkyne lactam **16**, the latter of which might eventually be prepared in homochiral form (vide infra).

The required 2-(3-chloropropyl) oxazole **14** was efficiently prepared by acylation of methyl alaninate with γ-chlorobutryl chloride (**20**), followed by cyclodehydration with P_2O_5 (20 g scale, 80%) (Scheme 2).[5a] It was not necessary to isolate the

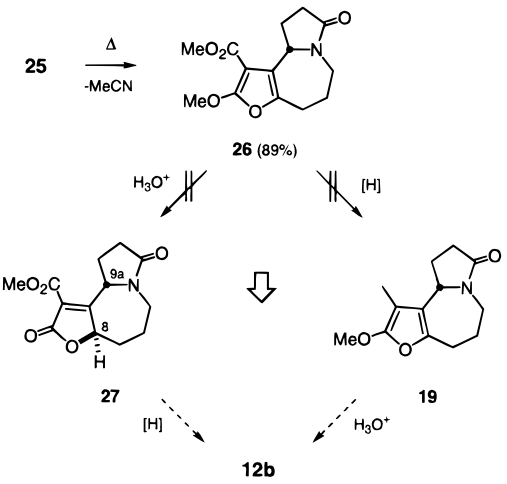
Scheme 2



intermediate amide **21**, which was formed in a high state of purity (cf. Experimental Section). Our initial alkylation experiments were then carried out with succinimide (**15**), which gave a 97% yield of the oxazole imide **22** upon treatment at 0 °C with NaH/DMF. These conditions turned out to be general for alkylation of **14** with a range of imide/lactam nucleophiles (vide infra). A number of routes were explored for converting the oxazole imide **22** to the desired alkyne oxazole **17**. By far the most convenient of these employed the methoxylactam **24**, which was derived from **22** by selective reduction with $NaBH_4$ (**22**→**23**),[7] followed by workup with MeOH/H^+ (72% overall yield).[8] Finally, $BF_3{\cdot}Et_2O$ catalyzed condensation of **24** with (1-propynyl)tributylstannane gave a 92% yield of the target oxazole **17**.[9] In similar fashion, we prepared the "activated" alkyne oxazole **25** (R = CO_2Me) by in situ activation of **23** with oxaloyl chloride, followed by trapping of the presumed acyliminium intermediate with lithio methyl propiolate. Alkyne **25** proved to be a useful model system for exploring subsequent Diels−Alder cyclizations.

In preliminary studies the activated alkyne oxazole **25** readily underwent the desired IMDA reaction. Thus, brief heating of **25** in toluene afforded an 89% yield of the furan ester **26**, which was isolated as a stable solid (Scheme 3). We also briefly

Scheme 3



explored the possibility that **26** might be further elaborated to the desired butenolide **12b** by either of two reaction pathways. The first of these involved chemoselective reduction of **26** to the corresponding methylfuran **19**, followed by acid-catalyzed hydrolysis. However, **26** proved to be remarkably stable to most reducing agents, and under forcing conditions suffered mainly decomposition. Similarly, an alternative route involving initial hydrolysis of **26** to the butenolide **27** also failed, due to the inertness of the furan ester **26** to even concentrated acid conditions. The stability of alkoxyfurans bearing strong electron withdrawing substituents has been noted previously.[5]

Not surprisingly, the "nonactivated" alkyne oxazole **17** was much less reactive toward the desired (Diels−Alder)−(*retro*-Diels−Alder) reaction sequence (Scheme 4). At temperatures

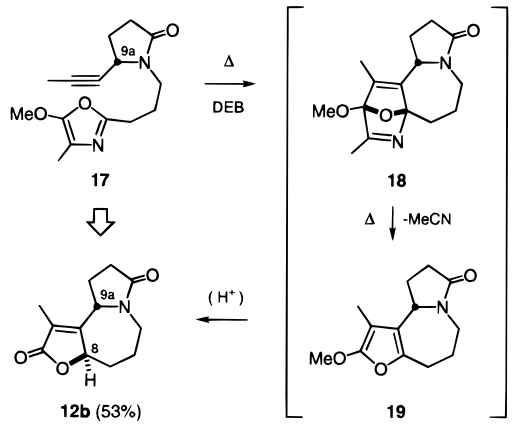
(7) Hart, D. J.; Sun, L.-Q.; Kozikowski, A. P. *Tetrahedron Lett.* **1995**, *36*, 7787.

(8) Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.

(9) See, for example: (a) Koot, W.-J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401. (b) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (c) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949. (d) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302.

up to 135 °C (ethylbenzene, reflux), **17** suffered mainly slow decomposition to intractable tars, with at best only trace amounts of **19** detectable by GC. Various efforts at catalyzing this reaction with Lewis acids also failed.[10] However, at higher temperatures we obtained mixtures of the anticipated methoxyfuran **19** as well as the butenolide **12b**, our projected precursor to stemoamide (**1**). In refluxing diethylbenzene (182 °C), this reaction afforded 50−55% of **12b** on gram scales and larger, together with only trace amounts of byproducts (see below). Although **19** was the major product by GC-MS analysis, it suffered rapid hydrolysis to **12b** upon attempted isolation. The difference in stability between methoxyfuran **19**, containing no electron withdrawing group, and methoxyfuran **26** is noteworthy.[5]

Scheme 4



In agreement with the calculations summarized in Figure 4, we could detect none of the epimeric cis-substituted butenolide **12a** upon hydrolysis of **19**. If formed at all, **12a** underwent spontaneous isomerization to **12b**. However, we did isolate and characterize a number of byproducts from the thermolysis of **17** (Figure 5). The most interesting of these were the diene **28** and the ring-opened ester **29**, both clearly derived by oxidation, and the unsaturated lactones **30** and **31**. These last two compounds are formally derived by methyl migration from −OMe to C_8 and C_{10}, respectively (stemoamide numbering). In addition to exhibiting the expected analytical and spectral properties, the identities of **28** and **29** were confirmed by chemical correlation.[11a] The structure of **30** was proven by X-ray analysis.[11b] Although each of these compounds was isolated in only 2−3% yield, their presence raised several mechanistic questions. In particular, the formation of **30** and **31** implicated a stepwise process for at least part of the cyclization sequence (control experiments demonstrated that neither of these compounds was formed upon thermolysis of **19**).

Taken together, these observations are consistent with an electron-transfer mechanism, in which oxazole **17** is in thermal equilibrium with the corresponding radical cation $\mathbf{17}^{\bullet+}$ (Scheme 5). Electrochemical studies indicate that this process should be feasible in the presence of mild oxidants ($E_{1/2}$Ox for **17** = 0.84 V at 25 °).[12a,b] Radical cation $\mathbf{17}^{\bullet+}$, which is activated toward cyclization,[13a] could then undergo an inverse electron demand Diels−Alder reaction,[13b] affording the furan radical cation **32**. This last material can now partition between several reaction

(10) Including, for example, $BF_3{\cdot}Et_2O$, Et_2AlCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, SiO_2, *p*-TsOH, Bu_3SnOMe, and others.

(11) (a) Upon treatment with $BF_3{\cdot}Et_2O$, methyl ester **29** was cleanly converted to butenolide **28**. (b) We are grateful to Dr. Victor G. Young, of The University of Minnesota, for carrying out the X-ray analysis of **30**.

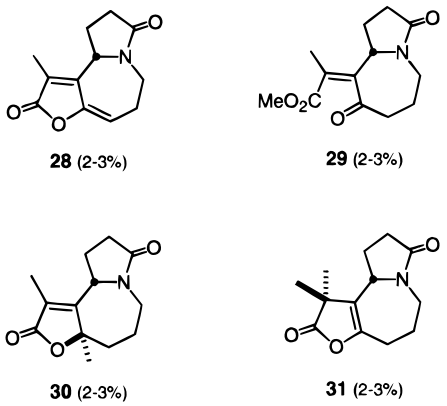
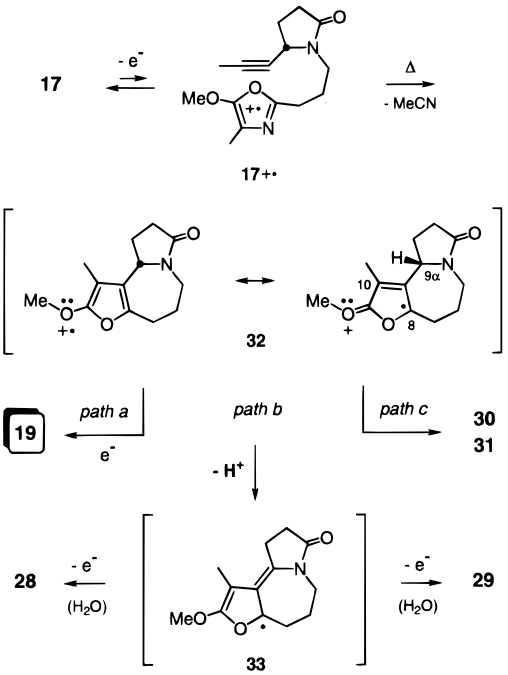


Figure 5. Byproducts from thermolysis of **17**.

pathways. Following *path a*, single electron reduction of **32** would afford the methoxyfuran **19**, a step that might propagate a chain process initiated by electron donation from oxazole **17**. Under ordinary circumstances this pathway is apparently highly favored, since **19** is by far the major product (see below, however). Following *path c*, both **30** and **31** could be derived by methyl radical abstraction (C_8 and C_{10}), followed by single electron reduction (a concerted 1,5-methyl shift to afford **30** directly is geometrically impossible; an ionic mechanism, involving Me^+, is equally unlikely). Finally, following *path b*, oxidation products **28** and **29** could arise by initial deprotonation at $C_{9\alpha}$, followed by oxidation of the labile radical **33** and subsequent hydrolysis.[12b]

Scheme 5

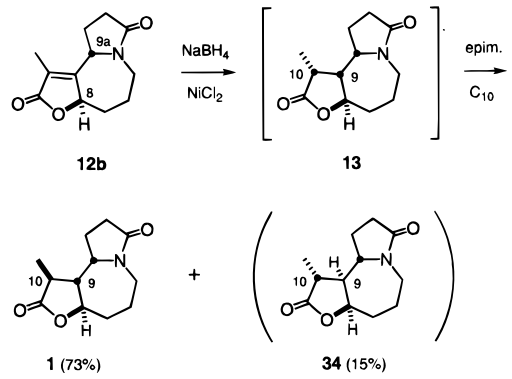


In principle, *path b* is subject to experimental verification, since the rate of formation of **28** and **29** should correlate roughly with the rate of proton abstraction from **32**. This turned out to be the case. Thus, under the usual conditions (base-free), the ratio of **19** to **29** after 48 h at 182 °C was >14:1 (GC-MS analysis with fluorene as internal standard). With added diisopropylethylamine this ratio decreased to 8:1 under identical conditions of time and temperature, and with suspended Na_2CO_3, **19** and **29** were formed in essentially equal amounts (1.3:

1). Finally, utilizing base-washed glassware (saturated NaOH in EtOH), **29** became the major product (**19**:**29** = 0.6:1.0), both by GC analysis and by isolation. Significant amounts of oxidized butenolide **28** were also formed. At present it is impossible to say whether the electron transfer mechanism represents the predominant reaction pathway, or simply operates in competition with the thermal Diels−Alder process. However, it is interesting to note that on large scales the cyclization of oxazole **17** to methoxyfuran **19** is facilitated by electron acceptors such as benzoquinone (cf. Experimental Section).[14]

The identity of butenolide **12b** was established by its highly characteristic NMR and IR spectra, and confirmed by its subsequent conversion to (±)-stemoamide (**1**). The remaining steps necessary to synthesize (±)-**1** involved (1) stereoselective cis-reduction of **12b** from the β-face (**12b**→**13**) and (2) epimerization at C_{10} (**13**→**1**, Scheme 6). Several reagents and

Scheme 6



catalyst systems were explored to effect this transformation. Butenolide **12b** was completely unreactive to standard hydrogenation conditions (PtO_2, Pd, or Ni/H_2), and was recovered unchanged upon treatment with various hydride reducing reagents. However, we obtained excellent results with the nickel boride catalyst derived from $NiCl_2$ and $NaBH_4$,[15a] which we have previously employed in the synthesis of methyllactones.[5,15b] When this reaction was carried out at −30 °C in MeOH we obtained a 73% yield of (±)-stemoamide (**1**) as a colorless crystalline solid, mp 184−85 °C [lit. mp for (−)-**1** 190−91 °C[4f] and 187−88 °C[4h]]. As in the case with **12** above (Scheme 4), we could detect none of the C_{10} epimer **13**, which underwent quantitative isomerization to (±)-**1**. The only other compound isolated from this reaction was a small amount of the cis-lactone **34** (15%), derived by α-face reduction of **12b** followed by epimerization at C_{10}.[15c] (±)-Stemoamide (**1**) thus prepared, in two steps from acetylenic oxazole **17** and 7 steps overall from **20** (Figure 6), had identical 500 MHz NMR, IR, and mass spectra as an authentic sample.[4f,16]

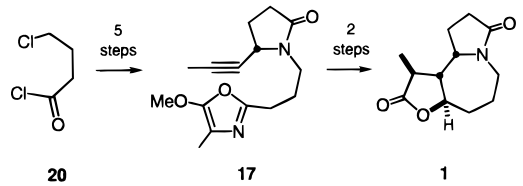
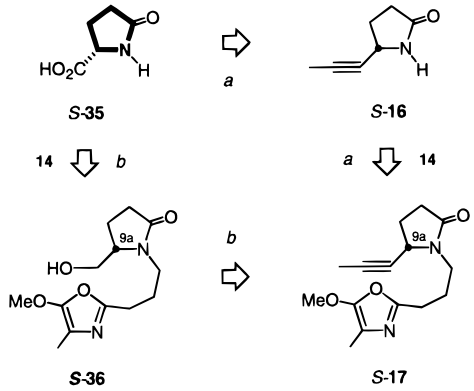


Figure 6. Summary of synthesis of (±)-**1**.

Synthesis of (−)-Stemoamide (1). To extend these studies to the synthesis of (−)-stemoamide (**1**), it was necessary to prepare the enantiomerically pure alkyne oxazole *S*-**17**. Two routes were explored for making this compound, both of which took advantage of the ready availability of L-pyroglutamic acid (*S*-**35**) (Scheme 7). One approach involved initial conversion of *S*-**35** to the alkyne lactam *S*-**16**, followed by alkylation with the 2-(3-chloropropyl) oxazole **14** (*path a*). Alternatively, the order of alkylation could be reversed, entailing preliminary construction of the oxazole lactam *S*-**36**, followed by elaboration of the propyne side chain (*path b*).

Scheme 7



The viability of *path a* was first tested with the racemic alkyne lactam **16**, which was prepared in 77% yield by condensation of 1-lithiopropyne with the known thiophenyl derivative **37**[17] ($ZnCl_2$ catalysis;[18] Scheme 8). Encouragingly, **16** afforded good-to-excellent yields of the displacement products **38** upon alkylation with a variety of electrophiles (**E** = Me, Bn, **14**). We then investigated the preparation of enantiomerically pure *S*-**16**. Excellent precedent for this synthesis existed in the work of Stevenson et al.,[19] who prepared the terminal alkyne derivative *S*-**40** by condensation of aldehyde *S*-**39** with diethylmethyldiazophosphonate (Gilbert's procedure).[20] Subsequent cleavage of the 2,4-dimethoxybenzyl protecting group in *S*-**40**,

(12) (a) One possible source of oxidant is trace amounts of air in the reaction mixture. Under 1 atm of air **17** undergoes rapid decomposition in refluxing diethylbenzene (182 °C). (b) Oxidation potentials were measured on 7 mM solutions of **17** in MeCN containing 0.1 M Bu_4NPF_6 as electrolyte, employing a Pt working electrode and a Ag/$AgNO_3$ reference electrode. We gratefully acknowledge Mr. John Porter and Professor Albert Fry, of Wesleyan University, for assistance in carrying out these experiments. Helpful discussions with Professor Kevin Moeller, of Washington University, St. Louis, are also acknowledged.

(13) (a) Yueh, W.; Bauld, N. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 871 and references therein. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793 and references therein.

(14) It is possible that the low oxidation potential of oxazoles plays a role in their exceptional reactivity as dienes in Diels−Alder reactions.[5a]

(15) (a) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420 and references therein. (b) Jacobi, P. A.; Frechette, R.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (c) During the course of this work, Kinoshita and Mori reported an independent synthesis of (−)-**1** employing butenolide (−)-**12b** (ref 4h). These authors reported a single product from the reduction of (−)-**12b** to give (−)-**1**. In our hands this reduction consistently produced an ∼5:1 mixture of **1** and **34**.

(16) We are grateful to Professor David R. Williams, of Indiana University, for providing us with NMR, IR, and mass spectra of authentic (−)-**1**.

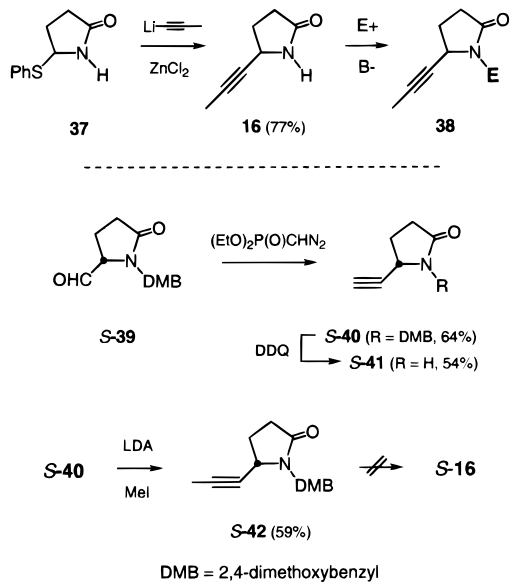
(17) (a) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552. (b) Nagasaka, T.; Abe, M.; Ozawa, N.; Kosugi, Y.; Hamaguchi, F. *Heterocycles* **1983**, *20* (6), 985.

(18) (a) Mori, S.; Iwakura, H.; Takeshi, S. *Tetrahedron Lett.* **1988**, 5391. (b) Olsen, R. K.; Kolar, A. J. *Tetrahedron Lett.* **1975**, 3579. (c) Scott, W. A.; Edwards, O. E.; Grieco, C.; Rank, W.; Sano, T. *Can. J. Chem.* **1975**, *53*, 463.

(19) McAlonan, H.; Stevenson, P. J. *Tetrahedron: Asymmetry* **1995**, *6*, 239.

(20) (a) Gilbert, J. C.; Weerasooniga, U. *J. Org. Chem.* **1979**, *44*, 4997. See also: (b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, **36**, 1379.

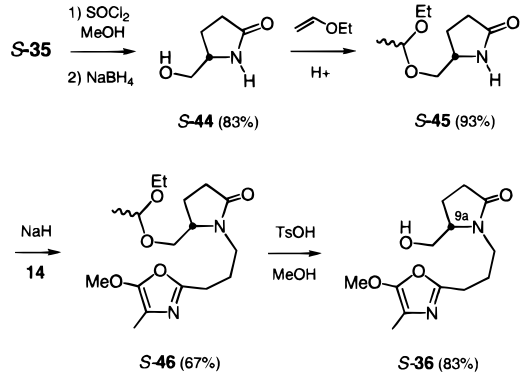
Scheme 8



although problematic, was ultimately accomplished in 54% yield using DDQ in refluxing $CHCl_3$ (*S*-**40** → *S*-**41**).[19] Following the literature procedure we prepared gram quantities of *S*-**40**,[19] which was readily converted to the propyne lactam *S*-**42** by methylation with MeI/LDA. In contrast to the case with *S*-**40**, however, we were unable to cleave the DMB protecting group in *S*-**42** without concomitant decomposition.[21a] Therefore, this route to *S*-**17** was not pursued further.

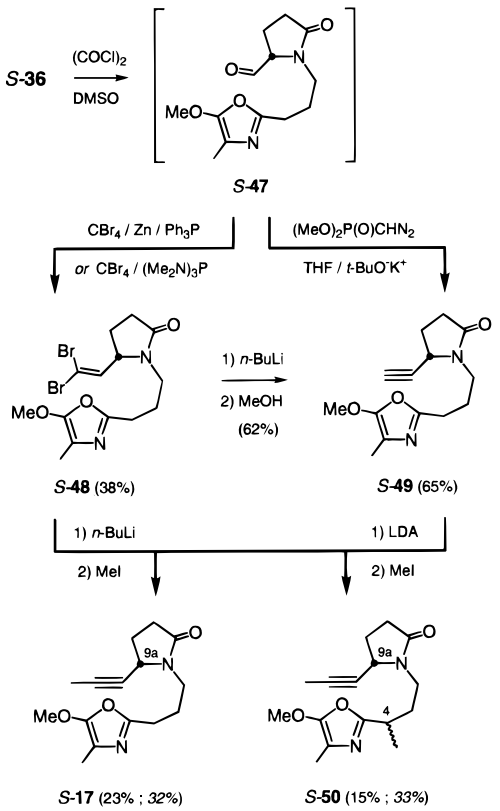
Increasing attention was now devoted to *path b* (cf. Scheme 7), for which a logical starting point was the known hydroxymethyl lactam *S*-**45** (Scheme 9).[22] This material was prepared in three steps beginning with L-pyroglutamic acid (*S*-**35**), by a route involving esterification ($SOCl_2$/MeOH, 90%), followed by ester reduction ($NaBH_4$/MeOH, 92%), and protection of the resulting primary alcohol with ethyl vinyl ether (H^+, 93%).[22] The desired oxazole alcohol *S*-**36** was then obtained in enantiomerically pure form by alkylation of *S*-**45** with the 2-(3-chloropropyl) oxazole **14** (NaH/DMF, 67%), followed by deprotection using TsOH in MeOH (83%). This synthesis was readily amenable to preparing *S*-**36** on multigram scales with no racemization.

Scheme 9



The remaining steps necessary to convert *S*-**36** to the required propyne derivative **S**-*17* were thought to be straightforward (Scheme 10). Overall, this transformation closely modeled our earlier synthesis of the alkyne lactam *S*-**42** (cf. Scheme 8). Thus, Swern oxidation of alcohol *S*-**36** proceeded normally to afford the aldehyde *S*-**47**,[19] which although unstable, was of sufficient purity for subsequent steps. One method for converting aldehyde *S*-**47** to the propyne lactam *S*-**17** made use of the Corey−Fuchs procedure,[23] which offered the possibility of effecting the desired transformation without isolation of an intermediate terminal alkyne. Following this protocol, aldehyde *S*-**47** was first converted to the dibromoalkene *S*-**48** by reaction with the ylide derived *in situ* from PPh_3 and CBr_4. Although this step was clean, the overall yield of *S*-**48** from the alcohol *S*-**36** was disappointingly low (38%). In part this was due to the high H_2O solubility of aldehyde *S*-**47**, which made its isolation from aqueous reaction mixtures tedious. Also, we had difficulty separating the dibromoalkene *S*-**48** from the large amounts of triphenylphosphine oxide ($O{=}PPh_3$) produced during the coupling process. Eventually we found that this last difficulty was eliminated through the use of hexamethylphosphorus triamide (HMPT) in place of PPh_3,[24] a modification that produced H_2O-soluble hexamethylphosphoramide (HMPA) as the byproduct.

Scheme 10



Our next experiments dealt with converting the dibromoalkene *S*-**48** to the propyne derivative *S*-**17**. This transformation was first effected by reacting the dibromoalkene *S*-**48** with 2 equiv of *n*-BuLi, followed by quenching with excess MeI (Scheme 10). Under these conditions the initially formed 1-lithioalkyne

(21) (a) Reagents explored included DDQ,[19] TFA,[21b] CAN,[21c] CrO_3/HOAc/H_2O,[21d] and *t*-BuOOH/Ru,[21e] among others. (b) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. Y. *J. Am. Chem. Soc.* **1985**, *107*, 1777. (c) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371. (d) Angyal, S. J.; James, K. *Carbohydr. Res.* **1970**, *12*, 147. (e) Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820.

(22) (a) Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449. (b) Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shirak, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838.

(23) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(24) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.

was directly alkylated to give *S*-**17** in a single step. However, this approach was only partly successful, affording a 23% yield of the anticipated product *S*-**17**, along with 15% of the bis-methylation product *S*-**50**. The structure of *S*-**50** was assigned on the basis of analytical and NMR spectral data, as well as literature precedent.[25] Particularly diagnostic was the presence of an sp^3 methyl doublet at δ 1.18 ppm, which collapsed to a singlet upon irradiation of the C_4 methine proton (stemoamide numbering). In an effort to avoid bis-methylation, we also investigated the conventional two-step conversion involving isolation of the terminal alkyne *S*-**49**. On small scales this compound was obtained in 62% yield by quenching the Corey−Fuchs intermediate with MeOH instead of MeI (*S*-**48** → *S*-**49**, Scheme 10).[23] However, for preparative purposes, *S*-**49** was more conveniently derived employing the Gilbert procedure ($[MeO]_2P(O)CHN_2$; cf. also Scheme 8),[20] which gave a 65% overall yield of the alkyne *S*-**49** from alcohol *S*-**36**. In addition to affording better yields, this methodology is less prone to causing epimerization at sensitive stereocenters.[19,26] With ample quantities of *S*-**49** now available, we were able to increase the yield in the alkylation step leading to *S*-**17** to 32%. However, despite numerous modifications in both reagents and conditions, bis-methylation to form *S*-**50** was always a competing reaction.

Finally, the transformation of *S*-**17** to enantiomerically pure (−)-stemoamide (**1**) followed in exactly analogous fashion to our earlier synthesis of (±)-**1**. This involved thermolysis of *S*-**17** to afford the enantiomerically pure butenolide (−)-**12b** (52%),[15c] followed by reduction with the $NaBH_4/NiCl_2$ reagent previously employed in the synthesis of (±)-**1** (Schemes 4 and 6). (−)-Stemoamide (**1**) thus obtained, in 73% yield, had identical physical and spectral properties as an authentic sample of (−)-**1**,[16] and closely matching optical rotation (cf. Experimental Section). For clarity, the complete reaction sequence leading from L-pyroglutamic acid (*S*-**35**) to (−)-stemoamide (**1**) is summarized in Figure 7.

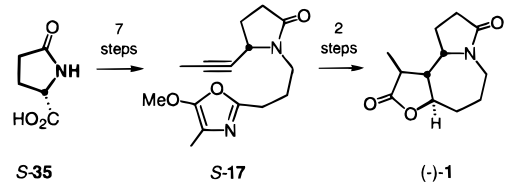


Figure 7. Summary of synthesis of (−)-**1**.

Summary

In this paper we describe a highly efficient synthesis of (±)-stemoamide (**1**), which was prepared in 7 steps, and ∼20% overall yield, from simple and inexpensive starting materials. All of the reactions utilized are readily amenable to scale-up, and the final product (±)-**1** was routinely produced in 0.4−1.0 g quantities. The key ring forming process involved an alkyne−oxazole (Diels−Alder)−(*retro*-Diels−Alder) reaction, which established the tricyclic skeleton of (±)-**1** in a single step. Of the four stereocenters in (±)-**1**, only C_9 was introduced by asymmetric induction (kinetic control). The remaining three centers (C_8, C_{9a}, C_{10}) were set on the basis of molecular mechanics calculations, which indicated that the "natural" configuration of (±)-**1** was the most stable. Our strategy then built upon thermodynamic control, in which each of these centers would be epimerizable at an appropriate stage of the synthesis (in the final product, only C_{10} is subject to equilibration). These same principles were readily extended to the synthesis of (−)-**1**, which although slightly longer (9 steps; ∼4% overall yield), also produced (−)-**1** as a single stereoisomer.[27a]

Experimental Section[27b]

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz and are expressed as ppm downfield from tetramethylsilane. All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen or argon.

Methyl 3-{1-[3-(5-Methoxy-4-methyl-1,3-oxazol-2-yl)propyl]-5-oxotetrahydro-1*H*-2-pyrrolyl}-2-propynoate (25). A solution of 250 mg (0.98 mmol) of **23** in 10 mL of CH_2Cl_2 was cooled to −78 °C, and was treated dropwise with 250 mg (1.97 mmol, 2 equiv) of oxalyl chloride. The resulting mixture was stirred for 30 min at −78 °C to afford a crude chlorolactam. At the end of this period the solvent was evaporated under reduced pressure (cold water bath), and the residue was dissolved in 4 mL of CH_2Cl_2. In a separate flask, 1-lithio methyl propriolate was generated by dropwise addition of 0.59 mL (1.47 mmol) of 2.5 M *n*-BuLi/hexane to a solution of 124 mg (1.47 mol) of methyl propiolate in 10 mL of CH_2Cl_2 maintained at −90 °C. The resulting solution was then treated dropwise, at −90 °C, with the crude chlorolactam solution described above, and the reaction was stirred for an additional 1 h at −90 °C. The reaction was then quenched with saturated NH_4Cl and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed to give 71 mg (23%) of **25** as a yellow oil: R_f 0.43 (5% MeOH/CH_2Cl_2); IR (neat) 2237, 1717, 1697, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89−2.09 (m, 2 H), 1.98 (s, 3 H), 2.10−2.25 (m, 1 H), 2.27−2.55 (m, 3 H), 2.61 (app t, J = 6.7 Hz, 2 H), 3.10−3.20 (m, 1 H), 3.66−3.78 (m, 1 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 4.47−4.51 (m, 1 H); LRMS *m*/*e* 279 (M^+ − 41), 264, 248, 232, 218, 204, 176, 160, 148, 132, 120.

Methyl 2-Methoxy-8-oxo-5,6,8,9,10,10a-hexahydro-4*H*-furo-[3,2-*c*]pyrrolo[1,2-*a*]azepine-1-carboxylate (26). A mixture of 69 mg (0.22 mmol) of alkyne **25** and a catalytic amount of *tert*-butylcatechol in 11 mL of dry toluene was heated at reflux for 2 h under an Ar atmosphere, and was then concentrated to dryness under reduced pressure. The residue was chromatographed (silica gel, 1% MeOH/CH_2Cl_2) to afford 54 mg (89%) of **26** as a colorless solid: R_f 0.41 (5% MeOH/CH_2Cl_2); IR (neat) 1691, 1602, 1372, 1094 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80−1.94 (m, 2 H), 2.06−2.20 (m, 1 H), 2.43 (app t, J = 8.0 Hz, 2 H), 2.54−2.67 (m, 2 H), 2.70−2.81 (m, 1 H), 2.88 (ddd, J = 7.0, 8.9, 15.8 Hz, 1 H), 3.80 (s, 3 H), 4.07 (s, 3 H), 4.17 (ddd, J = 3.6, 7.5, 14.0 Hz, 1 H), 4.87 (app t, J = 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 25.1, 27.7, 30.7, 40.1, 51.7, 58.4, 58.6, 90.8, 121.3, 122.4, 140.9, 164.0, 175.8; HRMS (EI) calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1107.

5-(1-Propynyl)-2-pyrrolidinone (16). A solution of 25.2 mL (63.1 mmol) of 2.5 M *n*-BuLi/hexane and 20 mg of triphenylmethane in 75 mL of dry THF was cooled to −78 °C, and was treated with propyne gas until the pink color was discharged. After the mixture was stirred for an additional 20 min, the reaction was treated dropwise with 83 mL (63.1 mmol, 1.0 equiv) of 0.5 M $ZnCl_2$/THF,[18] and the cooling bath was replaced with an ice−water bath. The mixture was then stirred for 30 min at 0 °C and the solvent was removed carefully under reduced pressure. The resulting gummy residue was diluted with 80 mL of dry benzene and treated dropwise, with vigorous stirring, with a solution of 1.19 g (6.20 mmol) of phenylthiolactam **37**[17] in 20 mL of dry benzene. The reaction was then heated for 90 min at 60 °C, cooled, and quenched with saturated NH_4Cl, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, and the crude product was purified by flash chromatography (eluent 33% hexane/EtOAc) to give 584 mg (77%) of **16** as a colorless

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(26) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

(27) (a) Financial support of this work by NSF Grant No. CHE-9424476 is gratefully acknowledged. (b) Additional spectral and analytical data are available in the Supporting Information section of ref 4i.

solid: R_f 0.28 (33% hexane/EtOAc); IR (neat) 3212, 2240, 1693, 1334, 1259, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3 H), 2.09−2.50 (m, 4 H), 4.31−4.38 (m, 1 H), 5.79 (br s, 1 H); LRMS *m*/*e* 123 (M^+), 108, 94, 79, 77, 68.

(5*S*)-1-(2,4-Dimethoxybenzyl)-5-(1-propynyl)tetrahydro-1*H*-2-pyrrolone (*S*-42). A total of 7.1 mL (11 mmol) of 1.54 M *n*-BuLi/hexane was added dropwise at −78 °C to a stirring solution of 1.7 mL (12 mmol) of *i*-Pr_2NH in 40 mL of freshly distilled THF. After addition was complete, the mixture was warmed to 0 °C and stirred for an additional 10 min to complete the formation of LDA. A solution consisting of 2.6 g (10 mmol) of alkyne *S*-**40**[19] and 2.1 mL (12 mmol) of HMPA in 20 mL of THF was added dropwise to the stirring LDA solution, and the resulting mixture was stirred for 10 min at −78 °C and then 30 min at 0 °C. A total of 3.1 mL (50 mmol) of CH_3I was then added in one portion. After the mixture was stirred an additional 1 h at 0 °C, the reaction was quenched with saturated NH_4Cl and diluted with 0.5 N HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (eluent 10% hexane/Et_2O) to give 1.6 g (59%) of *S*-**42** as a pale yellow oil: $[\alpha]_D^{25}$ −30.5 (*c* 2.08, MeOH); R_f 0.31 (Et_2O); IR (neat) 2939, 2836, 1689, 1612, 1508, 1411, 1208, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 2.1 Hz, 3 H), 1.96−2.07 (m, 1 H), 2.14−2.26 (m, 1 H), 2.29−2.40 (m, 1 H), 2.48−2.59 (m, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.10−4.15 (m, 1 H), 4.14 (d, J = 15 Hz, 1 H), 4.85 (d, J = 15 Hz, 1 H), 6.42−6.46 (m, 1 H), 6.45 (s, 1 H), 7.16 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.07, 27.0, 30.7, 39.7, 49.7, 55.9, 56.0, 77.9, 81.3, 99.0, 104.6, 117.7, 131.3, 159.3, 161.0, 174.6; HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1366.

(5*S*)-5-[(1-Ethoxyethyl)methyl]tetrahydro-1*H*-2-pyrrolone (*S*-45).[22] A solution consisting of 4.95 g (43 mmol) of hydroxymethyl lactam *S*-**44**,[22] 4.65 g (6.2 mL, 65 mmol, 1.5 equiv) of ethyl vinyl ether, and 141 mg (0.86 mmol) of trichloroacetic acid in 30 mL of dry chloroform was stirred for 4 h at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 5% MeOH/CH_2Cl_2) to give 7.45 g (93%) of *S*-**45**[22] as a colorless oil: $[\alpha]_D^{26}$ +24.1° (*c* 1.99, EtOH) {lit. $[\alpha]_D^{24}$ +20.8° (*c* 2.0, EtOH)[22a]}; R_f 0.41 (5% MeOH/CH_2Cl_2); IR (neat) 3228, 1698, 1134, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.30 (d, J = 5.4 Hz, 3 H), 1.68−1.81 (m, 1 H), 2.16−2.29 (m, 1 H), 2.35 (app t. J = 7 Hz, 2 H), 3.23−3.68 (m, 4 H), 3.81−3.88 (m, 1 H), 4.68−4.74 (m, 1 H), 5.98 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 20.2, 23.8, 30.3, 54.5, 61.7, 69.2, 100.3, 178.5; HRMS (CI) calcd for $C_9H_{18}NO_3$ (M + H) 188.1287, found 188.1285.

(5*S*)-5-[(1-Ethoxyethyl)methyl]-1-[3-(5-methoxy-4-methyl-1,3-oxazol-2-yl)propyl]tetrahydro-1*H*-2-pyrrolone (*S*-46). A solution of 2.02 g (10.8 mmol) of *S*-**45** in 5 mL of DMF was added dropwise to a stirring suspension of 561 mg (14.0 mmol, 1.3 equiv) of 60% NaH/mineral oil in 23 mL of DMF maintained at 0 °C. The reaction mixture was stirred for an additional 1 h at 0 °C, and was then treated dropwise with a solution of 2.25 g (11.9 mmol, 1.1 equiv) of the 2-(3-chloropropyl) oxazole **14** in 2 mL of DMF. The resulting yellow mixture was then stirred at 70 °C for 24 h. At the end of this period the reaction was concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (33% hexane/EtOAc) to give 2.46 g (67%) of *S*-**46** as a pale yellow oil: $[\alpha]_D^{25}$ +15.0 (*c* 2.04, EtOH); R_f 0.43 (5% MeOH/CH_2Cl_2); IR (neat) 2977, 2935, 1682, 1235, 1134, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7 Hz, 3 H), 1.25 (d, J = 5.5 Hz, 3 H), 1.78−2.45 (m, 6 H), 1.96 (s, 3 H), 2.58 (t, J = 7.6 Hz, 2 H), 3.02−3.11 (m, 1 H), 3.35−3.75 (m, 6 H), 3.84 (s, 3 H), 4.63−4.72 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 16.8, 21.1, 23.5, 26.1, 27.5, 31.7, 41.7, 58.8, 62.5, 67.0, 67.3, 101.2, 112.7, 155.9, 177.0; HRMS (EI) calcd for $C_{17}H_{28}N_2O_5$ 340.1998, found 340.1996.

(5*S*)-5-(Hydroxymethyl)-1-[3-(5-methoxy-4-methyl-1,3-oxazol-2-yl)propyl]tetrahydro-1*H*-2-pyrrolone (*S*-36). A solution of 2.78 g (8.17 mmol) of *S*-**46** and a catalytic amount of *p*-TsOH in 15 mL of MeOH was stirred for 9 h at room temperature. The reaction was then concentrated under reduced pressure, and the crude product was purified by flash chromatography (eluent 5% MeOH/CH_2Cl_2) to give 1.83 g (83%) of *S*-**36** as a colorless oil: $[\alpha]_D^{25}$ +20.7° (*c* 1.78, EtOH); R_f 0.27 (5% MeOH/$CHCl_3$); IR (neat) 3351, 1675, 1459, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81−2.49 (m, 6 H), 2.00 (s, 3 H), 2.63−2.78 (m, 2 H), 3.31−3.51 (m, 2 H), 3.64−3.85 (m, 3 H), 3.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 22.8, 25.9, 27.2, 32.0, 42.1. 61.9, 62.7, 64.7, 112.4, 156.2, 177.7; HRMS (EI) calcd for $C_{13}H_{20}N_2O_4$ 268.1423, found 0.268.1424.

(2*S*)-1-[3-(5-Methoxy-4-methyl-1,3-oxazol-2-yl)propyl]-5-oxotetrahydro-1*H*-2-pyrrolecarbaldehyde (*S*-47). A solution of 988 mg (0.68 mL, 7.78 mmol) of $(COCl)_2$ in 15 mL of dry CH_2Cl_2 was cooled to −78 °C with stirring, and was treated dropwise with 608 mg (0.55 mL, 7.78 mmol, 1.0 equiv) of dry DMSO. After addition was complete stirring was continued at −78 °C for an additional 15 min, and the reaction was then treated dropwise over 10 min with a solution of 1.74 g (6.49 mmol) of alcohol *S*-**36** in 5 mL of dry CH_2Cl_2. After the mixture was stirred an additional 1 h at −78 °C, the reaction was treated slowly with 4.52 mL (32.4 mL) of freshly distilled NEt_3, and the resulting creamy suspension was allowed to warm to room temperature. The reaction was then diluted with 5 mL of H_2O and 10 mL of 0.1 N HCl (vigorous stirring), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 1.03 g of aldehyde *S*-**47** as an unstable yellow oil, which was utilized immediately for the next step: R_f 0.31 (5% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.44 (m, 4 H), 1.98 (s, 3 H), 2.62 (t, J = 7 Hz, 2 H), 3.05−3.16 (m, 2 H), 3.70−3.81 (m, 2 H), 3.38 (s, 3 H), 4.18−4.23 (m, 1 H), 9.61 (s, 1 H).

(5*S*)-5-(2,2-Dibromovinyl)-1-[3-(5-methoxy-4-methyl-1,3-oxazol-2-yl)propyl]tetrahydro-1*H*-2-pyrrolone (*S*-48). **Method A:** A mixture consisting of 288 mg (4.41 mmol) of zinc dust, 1.16 g (4.41 mmol) of Ph_3P, and 1.46 g (4.41 mmol) of CBr_4 in 15 mL of dry CH_2Cl_2 was stirred for 16 h at room temperature. A solution of 587 mg (2.20 mmol) of crude aldehyde *S*-**47** in 5 mL of CH_2Cl_2 was added to the mixture, and the reaction was stirred for an additional 18 h at room temperature. The resulting mixture was then filtered through a short plug of SiO_2 and concentrated under reduced pressure (two repetitions), and the residue was purified by flash chromatography (eluent 1% *i*-PrOH/$CHCl_3$) to give 580 mg (38% from alcohol *S*-**36**) of *S*-**48** as a colorless oil.

Method B: A total of 2.2 mL (12 mmol) of hexamethylphosphotriamide (HMPT) was added dropwise, and with vigorous stirring, to a solution of 2.0 g (6.05 mmol) of CBr_4 in 50 mL of THF maintained at −30 °C. After being stirred an additional 10 min, the resulting mixture was treated dropwise with a solution of 322 mg (1.2 mmol) of aldehyde *S*-**47** in 6 mL of THF, and the reaction was allowed to warm to 0 °C over a period of 1 h with stirring. The reaction was then quenched with saturated $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent 1% *i*-PrOH/$CHCl_3$) to give 214 mg (24% from alcohol *S*-**36**) of dibromide *S*-**48** as a colorless oil: $[\alpha]_D^{26}$ +39.7° (*c* 1.85, EtOH); R_f 0.46 (5% *i*-PrOH/$CHCl_3$); IR (neat) 1691, 1414, 1329, 1277 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.84 (m, 1 H), 1.86−2.06 (m, 2 H), 1.99 (s, 3 H), 2.21−2.46 (m, 3 H), 2.62 (t, J = 7.6 Hz, 2 H), 2.96 (ddd, J = 5.4, 8, 14 Hz, 1 H), 3.63 (dt, J = 8, 14.3 Hz, 1 H), 3.87 (s, 3 H), 4.35−4.42 (m, 1 H), 6.32 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 24.5, 25.1, 26.4, 30.2, 40.9, 60.5, 61.6, 93.4, 111.6, 138.1, 154.5, 155.1, 174.9; HRMS (EI) calcd for $C_{14}H_{18}Br_2N_2O_3$ 419.9684, found 419.9684.

(5*S*)-5-Ethynyl-1-[3-(5-methoxy-4-methyl-1,3-oxazol-2-yl)propyl]-tetrahydro-1*H*-2-pyrrolone (*S*-49). A suspension of 521 mg (4.64 mmol) of potassium *tert*-butoxide in 9 mL of THF was cooled to −78 °C, and was treated dropwise, over a period of 10 min, with a solution of 697 mg (4.64 mmol) of dimethyl (diazomethyl)phophonate in 12 mL of dry THF. After the mixture was stirred an additional 10 min at

−78 °C, the reaction was treated dropwise with a solution of 1.03 g (3.87 mmol) of aldehyde *S*-**47** in 11 mL of THF. Stirring was continued for 7 h at −78 °C, and the reaction mixture was then quenched with ice water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent 1% *i*-PrOH/$CHCl_3$) to give 658 mg (65% from alcohol *S*-**36**) of *S*-**49** as a colorless oil: $[\alpha]_D^{25}$ −10.5° (*c* 1.6, EtOH), −14.4° (*c* 1.38, MeOH); R_f 0.39 (5% *i*-PrOH/$CHCl_3$); IR (neat) 3224, 2945, 2110, 1682, 1576, 1416, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92−2.19 (m, 4 H), 2.01 (s, 3 H), 2.27−2.55 (m, 2 H), 2.40 (d, J = 2.3 Hz, 1 H), 2.64 (app t, J = 7 Hz, 2 H), 3.21 (ddd, J = 5.5, 7.7, 14 Hz, 1 H), 3.72 (dt, J = 7.8, 14 Hz, 1 H), 3.89 (s, 3 H), 4.35−4.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 24.9, 26.4, 26.6, 30.2, 40.8, 49.4, 61.5, 74.1, 81.8, 111.6, 154.6, 155.1, 174.7; HRMS (EI) calcd for $C_{14}H_{18}N_2O_3$ 262.1317, found 262.1316.

(5*S*)-1-[3-(5-Methoxy-4-methyl-1,3-oxazol-2-yl)propyl]-5-(1-propynyl)tetrahydro-1*H*-2-pyrrolone (*S*-17). A solution of 196 mg (0.75 mmol) of alkyne *S*-**49** in 10 mL of dry THF was cooled to −78 °C with stirring, and was treated dropwise with a solution of 0.75 mL (1.50 mmol, 2 equiv) of 2 M LDA in heptane/THF/ethylbenzene. The resulting mixture was stirred for an additional 2.5 h at −78 °C, and was then treated with 530 mg (0.23 mL, 3.74 mmol) of MeI and 267 mg (0.26 mL, 1.50 mmol, 2 equiv) of hexamethylphosphoramide. After being stirred an additional 3.5 h at −78 °C, the reaction mixture was quenched with ice water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent 1% *i*-PrOH/$CHCl_3$) to yield 66 mg (32%) of *S*-**17** and 72 mg (33%) of the bis-methylation product (*S*-**50**) as pale yellow oils.

***S*-17**: $[\alpha]_D^{25}$ −21.5 (*c* 1.18, MeOH); R_f 0.36 (5% *i*-PrOH/$CHCl_3$); identical IR and NMR data as (±)-**17** described above; HRMS (EI) calcd for $C_{15}H_{20}N_2O_3$ 276.1474, found 276.1473.

***S*-50**: R_f 0.40 (5% *i*-PrOH/$CHCl_3$); IR (neat) 2361, 2342, 1694, 1419, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 7.1 Hz, 3 H), 1.81 (s, 3 H), 1.78−2.08 (m, 3 H), 2.01 (s, 3 H), 2.23−2.39 (m, 1 H), 2.55−2.69 (m, 1 H), 2.63 (app t, J = 7 Hz, 2 H), 3.12−3.23 (m, 1 H), 3.64−3.75 (m, 1 H), 3.89 (s, 3 H), 4.23−4.31 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.97, 10.4, 16.3, 25.1, 26.5, 36.0, 41.0, 48.0, 53.9, 61.6, 73.5, 81.3, 111.7, 155.0, 177.7, 186.9; HRMS (EI) calcd for $C_{16}H_{22}N_2O_3$ 290.1630, found 290.1629.

(3a*R*,10a*S*)-1-Methyl-3a,4,5,6,8,9,10,10a-octahydro-2*H*-furo-[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8-dione [(−)-12b]. This material was prepared in 52% yield from 65 mg of *S*-**17**, following an identical procedure to that descrtibed above for (±)-**12b**.

(−)-12b: colorless solid, mp 166−67 °C (lit.[4h] mp 127−29 °C); $[\alpha]_D^{24}$ −261.05° (*c* 1.33, MeOH) {lit.[4h] $[\alpha]_D^{27}$ −246.3° (*c* 0.63, MeOH)}; R_f 0.34 (5% $CH_3OH/CHCl_3$); identical IR and NMR data as (±)-**12b** described above; HRMS (EI) calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1052 Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.81; N 6.28.

(−)-Stemoamide [(−)-1]: This material was prepared in 73% yield from 24 mg of (−)-**12b**, following an identical procedure to that descrtibed above for (±)-**1**.

(−)-1: colorless solid, mp 186−187 °C (lit. mp 187−88 °C[4h] and 190−91 °C[4f]); $[\alpha]_D^{25}$ −183.5° (*c* 1.36, MeOH) {lit. $[\alpha]_D^{30}$ −219.3° (*c* 0.50, MeOH);[4h] $[\alpha]_D^{26}$ −141° (*c* 0.19, MeOH)[4f] and −181° (*c* 0.89, MeOH);[4f] R_f 0.38 (5% *i*-PrOH/$CHCl_3$); identical IR and NMR data as (±)-**1** described above. HRMS (EI) calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1209; Anal. Calcd for C, 64.54; H, 7.68; N, 6.28. Found: C, 64.63; H, 7.72; N, 6.30.

Supporting Information Available: Copies of ^1H- and ^{13}C-NMR spectra for compounds **16**, **25**, **26**, *S*-**36**, **37**, *S*-**40**, *S*-**41**, (*S*-**44**)−(*S*-**46**), and (*S*-**48**)−(*S*-**50**) (PDF).[27b] This material is available free of charge via the Internet at http://pubs.acs.org.

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