Toward the Synthesis of Biologically Important Chlorins, Isobacteriochlorins, and Corrins. Cyclic Enamides from Acetylenic Amides

Peter A. Jacobi,* Harry L. Brielmann, and Sheila I. Hauck

Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06459-0180

Received March 1, 1996[⊗]

Cyclic enamides **1** of a type useful in the synthesis of naturally occurring chlorins, isobacteriochlorins, and corrins have been prepared by a process involving 5-*exo*-*dig* cyclization of the appropriate acetylenic amides **11**. The desired cyclization is catalyzed by either *n*-Bu_4NF or $LiAl(NHBn)_4$.

Introduction

Cyclic enamides of type **1** are an important functionality in natural products chemistry, and they have been utilized in either free or protected form **2** in the synthesis of species such as as prostaglandin analogs,[1a] γ-lactam antibiotics,[1b] peptide mimics,[1c] angiotensin II antagonists,[1d] and other biologically active compounds (Figure 1).[1e] In addition, they form the skeleton of macrocyclic tetrapyrroles of the chlorin, isobacteriochlorin, and corrin oxidation level. Members of the latter class serve important biological functions as vitamins, cofactors, and light-absorbing pigments, and the stereochemical complexities associated with such ring systems can be enormous.[1f]

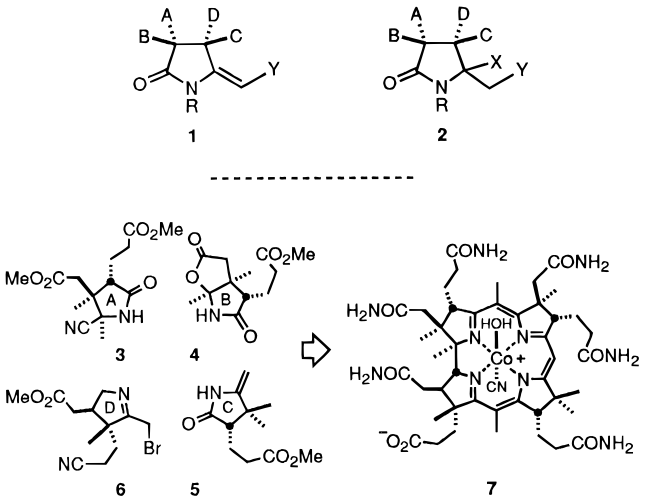
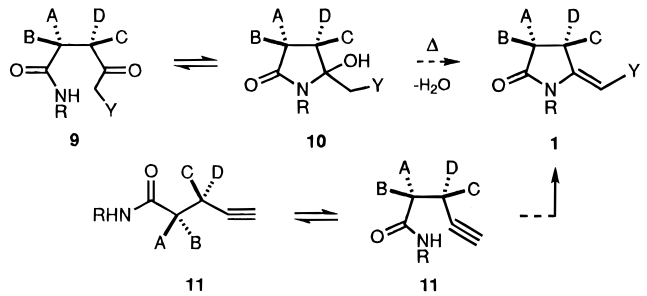


Figure 1.

A landmark study in this area was the early work of Woodward and Eschenmoser,[2b] which culminated in the total synthesis of cobyric acid (**7**), a known precursor to vitamin B_{12} (**8**) (Figure 1), perhaps the most complicated of the naturally occurring corrins. Subsequently, Eschenmoser *et al*. published an improved synthesis of **7** that made elegant use of enamide derivatives **3**−**5** and pyrroline **6** for assembling the corrin skeleton.[2a] Not surprisingly, highly substituted ring systems of type **3**−**6** are themselves a significant synthetic challenge. For example, the simplest member of this group, enamide **5**, was prepared in nine steps from acyclic starting materials in an overall yield of ∼2% (including resolution).[2a] Alternatively, **5** could be derived in seven steps by degradation of (+)-camphor.[2b,c] Similar difficulties have been encountered in the syntheses of related enamides of type **1**, particularly those in which Y = H.

Numerous strategies have been employed for the synthesis of enamide derivatives of general structure **1**.[3] However, most approaches make use of keto amide cyclizations of type **9** → **10**, in which carbinolamide formation is followed by dehydration (Scheme 1). This last step frequently requires forcing conditions (T > 150 °C), which can cause decomposition of the highly sensitive **1**. Also, substituted keto amides of type **9** are themselves difficult to prepare, in particular in enantiomerically pure form. In this paper we describe an alternative strategy for the synthesis of enamides **1** (Y = H, CO_2Me) that involves direct cyclization of acetylenic amides of type **11**. This route has the advantage of proceeding under mild conditions from readily available starting materials (*vide infra*),[4,5a] and it has been utilized in efficient syntheses of two potential ring C precursors of vitamin B_{12}.[4c]

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1996.

(1) (a) Barco, A.; Benetti, S.; Pollini, G. P. *J. Org. Chem.* **1979**, *44*, 1734. (b) Hashiguchi, S.; Natsugari, H.; Ochiai, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2345. (c) Abell, A. D.; Taylor, J. M. *J. Org. Chem.* **1993**, *58*, 14. (d) Murray, W. V.; Lalan, P.; Gill, A.; Addo, M. F.; Lewis, J. M.; Lee, D. K. H.; Wachter, M. P.; Rampulla, R.; Underwood, D. C. *Bioorg. Med. Chem. Lett.* **1993**, *369*, 785. (e) James, G. D.; Pattendon, G.; Mills, S. D. *Tetrahedron Lett.* **1985**, *26*, 3617. (f) Flitsch, W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, Inc.: San Diego, 1988; Vol. 43, p 74 (Hydrogenated Porphyrin Derivatives: Hydroporphyrins).

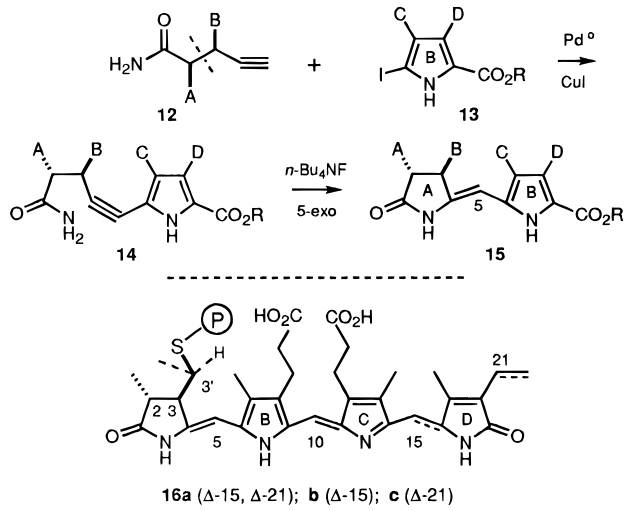
(2) (a) Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410 and references cited therein. See also: (b) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519; (c) **1971**, *25*, 283; (d) **1973**, *33*, 145. (e) Eschenmoser, A. *Q. Rev.* **1970**, *24*, 366. (f) Eschenmoser, A. *Pure Appl. Chem. Suppl.* **1971**, *2*, 69. (g) Eschenmoser, A. *Naturwissenshaften* **1974**, *61*, 513. (h) Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 5.

S0022-3263(96)00428-8 CCC: $12.00

Discussion and Results

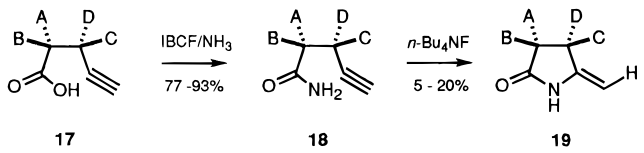
We have recently reported that Pd(0)-mediated coupling of acetylenic amides **12** with iodopyrroles **13** affords excellent yields of acetylenic pyrroles of type **14**,[6,7] which upon fluoride ion-catalyzed 5-*exo*-*dig* cyclization gave dihydropyrromethenones **15** having the 5(*Z*)-stereochemistry (Scheme 2).[4] These materials are attractive precursors for biologically important linear tetrapyrroles such as phytochrome (**16a**), phycocyanin (**16b**), and phycoerythrin (**16c**).[8] The utility of this approach stems partly from the fact that a wide variety of ring-A synthons **12** (and *ent*-**12**) are available by Nicholas−Schreiber reaction of chiral ester enolates with cobalt-stabilized propargylic cations (dashed line in **12**).[4,5] We expected that a similar approach could be utilized for the synthesis of acetylenic amides of type **11** (*cf.* Scheme 1).

Scheme 2



The conversion of **14** to **15** provided reasonable precedent for the desired 5-*exo*-*dig* cyclization leading from acetylenic amide **11** to monocyclic enamide **1** (*cf.* Scheme 1). However, for the case of **14** → **15**, intramolecular nucleophilic addition is facilitated by the pyrroloester substituent, which renders the alkyne relatively electron deficient. It was uncertain whether such cyclizations would be possible with simple unactivated alkynes. In order to study this question, we prepared a series of simple N-unsubstituted amides **18**, which in the case of **18a**−**c** were derived in 77−93% yield from the known carboxylic acids **17a**−**c** using isobutyl chloroformate (IBCF) and NH_3 (Scheme 3).[9] Enantiomerically pure

Scheme 3



a: A-D = H. **b**: A,B = Me; C,D = H. **c**: A,B = H; C,D = Me.
d: A = H; B,C,D = Me. **e**: A,C = Me; B,D = H. **f**: A,C = H; B,D = Me

amides **18e**,**f** and racemic amide **18d** were prepared in excellent overall yield as previously described for acetylenic amides **1** using the Nicholas−Schreiber methodology.[4,5a] Acetylenic amides **18** turned out to be relatively unreactive toward direct cyclization to enamides **19**, affording at best a 10−20% yield of **19d** and a 5−10% yield of **19c** upon heating with *n*-Bu_4NF in refluxing THF (65−67 °C, 24−48 h).[4b] It appears that cyclizations of this type are feasible only with highly substituted substrates, in particular those containing geminal dimethyl substituents (Thorpe−Ingold effect[10]). No cyclization occurred with **18a** or **18e**,**f**. Also, higher reaction temperatures and/or longer reaction times led to substantial decomposition. These results are in marked contrast to those obtained with activated alkynes of type **14**, which afforded dihydropyrromethenones **15** in >85% yields under identical conditions (*cf.* Scheme 1).[4b] In the case of **14**, the pyrroloester substituent undoubtedly facilitates nucleophilic addition to the alkyne.

We next explored the possibility that enamides **19** might be derived by Pd(II)-catalyzed cyclization of **18** to vinyl-Pd species **20**, followed by protonolysis of the carbon−Pd bond (Scheme 4).[11a−c] Since palladium is not reduced in such cyclizations, no cooxidant is required. Many such examples have been documented with related systems,[11a−c] and we expended considerable effort in investigating this route. However, this direct approach was precluded by the extreme acid sensitivity of terminal enamides **19**, which rapidly decompose at pH < 4. Equally discouraging results were obtained with a wide range of reagents that have been successfully employed

(3) See, for example: (a) Walton, E. *J. Chem. Soc.* **1940**, 439. (b) Schulte, K. E.; Reisch, J. *Arch. Pharm.* **1959**, *292*, 51. (c) Schulte, K. E.; Reisch, J.; Hobl, R. *Arch. Pharm.* **1960**, *293*, 687. (d) Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 490; **1969**, *8*, 343. (e) Scheffold, R.; Löliger, J.; Blaser, H.; Geisser, P. *Helv. Chim. Acta* **1975**, *58*, 49. (f) Gossauer, A.; Kuhne, G. *Liebigs Ann. Chem.* **1977**, 664. (g) Cannizarro, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316. (h) Ribo, J. M.; Serra, X. *Monatsh. Chem.***1986**, *117*, 185. (i) Jones, R. C. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S. *J. Chem. Soc, Perkin Trans. 1* **1990**, 1959. (j) Micklefield, J.; Mackman, R. L.; Aucken, C. J.; Beckmann, M.; Block, M. H.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1993**, *275*. (k) Abell, A. D.; Oldham, M. D.; Taylor, J. M. *J. Org. Chem.* **1995**, *60*, 1214 and references cited therein. See also refs 4, 7a, 8a,e, and 2a,b.

(4) (a) Jacobi, P. A.; Guo, J. *Tetrahedron Lett.* **1995**, *36*, 2717. (b) Jacobi, P. A.; Guo, J.; Zheng, W. *Tetrahedron Lett.* **1995**, *36*, 1197. Preliminary communication: (c) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *Tetrahedron Lett.* **1995**, *36*, 1193. (d) Jacobi, P. A.; Rajeswari, S. *Tetrahedron Lett.* **1992**, *33*, 6231; (e) **1992**, *33*, 6235. (f) Jacobi, P. A; DeSimone, R. W. *Tetrahedron Lett.* **1992**, *33*, 6239. See also: (g) Jacobi, P. A.; Buddhu, S. C. *Tetrahedron Lett.* **1988**, *29*, 4823. (h) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, in press.

(5) (a) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. (b) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163.

(6) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(7) (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587. (c) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1971**, 502. See also: (d) Jacobi, P. A.; Cai, G. *Heterocycles* **1993**, *35*, 1103.

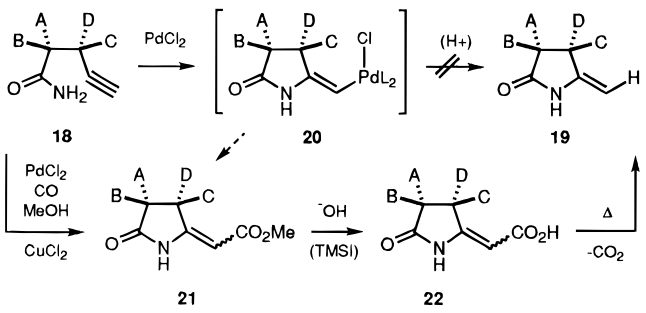
(8) (a) Gossauer, A.; Miehe, D. *Liebigs Ann. Chem.* **1974**, 352. (b) Weller, J.-P.; Gossauer, A. *Chem. Ber.* **1980**, *113*, 1603. (c) Gossauer, A.; Weller, J.-P. *Chem. Ber.* **1978**, *111*, 486. (d) Schoenleber, R.; Kim, Y.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 2645. (e) Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024 and references cited therein.

(9) (a) Acetylenic acid **17a**: Aldrich Chemical Co., Milwaukee, WI. (b) Acetylenic acid **17b**: Magnus, P.; Slater, M. J.; Principe, L. M. *J. Org. Chem.* **1989**, *54*, 5148. (c) Acetylenic acid **17c**: Easton, N. R.; Dillard, R. D. *J. Org. Chem.* **1962**, *27*, 3602. (d) Acetylenic acid **17d**: Crombie, L.; Mackenzie, K. *J. Chem. Soc.* **1958**, 4417.

(10) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. For more recent interpretations of this effect, see: (b) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319 and references cited therein. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

(11) Amide cyclizations: (a) Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H. *Tetrahedron Lett.* **1985**, *26*, 5963. (b) Knapp, S.; Levorse, I. *J. Org. Chem.* **1988**, *53*, 4006. (c) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856. (d) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. See also refs 1 and 8c.

Scheme 4



a: A-D = H. **b**: A,B = Me; C,D = H. **c**: A,B = H; C,D = Me.
d: A = H; B,C,D = Me. **e**: A,C = Me; B,D = H. **f**: A,C = H; B,D = Me

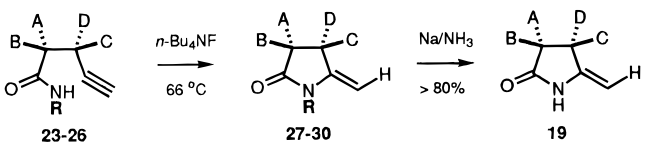
Compd (% yield)	**a**	**b**	**c**	**d**	**e**	**f**
21	61%	51%	96%	72%	50%	50%
22	0%	---	90%	93%	0%	0%
19	---	---	99%	97%	---	---

for the cyclization of related amides,[11] amines,[12] carbamates,[13] and acids.[14] In many cases no reaction was observed at all. Moreover, when cyclization did occur, it often took place with participation of the amide carbonyl group to produce lactones.

These difficulties were first circumvented with our finding that **18** afforded moderate to excellent yields of stable enamide esters **21** upon treatment with the reagent system $PdCl_2$/CO/$CuCl_2$/MeOH (Scheme 4). Tsuji *et al.* have employed similar conditions for effecting methoxycarbonylation of terminal alkynes,[15] and it is possible that acetylenic esters are intermediates in the formation of **21**. However, at present we favor a mechanism in which **20** undergoes CO complexation, followed by migratory insertion,[16] and acyl substitution with MeOH (*cf.* dashed arrow in Scheme 4). Stoichiometric quantities of $CuCl_2$ were necessary in order to reoxidize Pd(0), obtained by reductive elimination of HCl, to Pd(II). Finally, we expected that esters **21** would afford enamides **19** by a two-step sequence involving hydrolysis to acids **22** followed by decarboxylation, and in certain cases this procedure worked well. Thus, LiOH hydrolysis of esters **21c**,**d** afforded 90−93% yields of carboxylic acids **22c**,**d**, which upon brief thermolysis gave >95% yields of the corresponding enamides **19c**,**d**. However, the efficiency of this process depended in a critical fashion upon the substitution pattern of esters **21**. With **21c**,**d** the enamide double bond is shielded by the neighboring geminal methyl groups (*i.e.*, C,D = Me), and ester hydrolysis is clean. In contrast, however, with **21a**,**b** and **21e**,**f** all attempts at ester hydrolysis led to complex mixtures of products, which appeared to arise by competing Michael addition followed by ring opening.

Much more satisfactory results were obtained with acetylenic *N*-benzylamides of type **23**−**25** (R = Bn, 4-MeOBN, and 3,4-di-MeOBn) and methyl carbazates **26**, which underwent cyclization to enamides **27**−**30** at a greatly enhanced rate with *n*-Bu_4NF (TBAF) (Scheme 5).

Scheme 5



a: A-D = H. **b**: A,B = Me; C,D = H. **c**: A,B = H; C,D = Me.
d: A = H; B,C,D = Me. **e**: A,C = Me; B,D = H. **f**: A,C = H; B,D = Me

Compd (% yield)	**a**	**b**	**c**	**d**	**e**	**f**
23 --> **27** (**R**=Bn)	84%	99%	98%	99%	92%	93%
24 --> **28** (**R**=4-MeOBn)	---	82%	99%	98%	---	---
25 --> **29** (**R**=3,4-di-MeOBn)	---	89%	99%	99%	---	---
26 --> **30** (**R**=NMeCO_2Me)	---	---	90%	---	---	---

For example, amides **23b**−**f** (R = Bn) gave essentially quantitative yields of the corresponding enamides **27b**−**f** upon heating for 3 h with 1.0 equiv of TBAF at 66 °C (THF). Even the least reactive member of this series, **23a** (A−D = H), afforded >80% yields of enamide **27a**. By way of comparison, N-unsubstituted acetylenic amides **18a**−**f**, which have otherwise identical substituents, afforded at best only trace amounts of enamides **19a**−**f** after heating for 24 h with 6.0 equiv of TBAF (*cf.* Scheme 3). Similar rate dependencies on the N-substitution pattern have been observed with related amide and carbamate cyclizations.[11d,13] In analogous fashion, benzylamide **24c** (R = 4-MeOBn) gave a 99% yield of enamide **28c**, and benzylamide **25c** (R = 3,4-di-MeOBn) gave 99% of enamide **29c**. Electron-rich aromatic rings of the type found in enamides **28** (R = 4-MeOBn) and **29** (R = 3,4-di-MeOBn) have the potential advantage of facilitating *N*-benzyl cleavage under either oxidative or solvolytic conditions.[17a] Similarly, methyl carbazates **30** should be particularly susceptible to both reductive[17a] and photochemical cleavage.[4g,17b] In any event, enamides **27b**−**d** (R = Bn) gave >80% yields of the corresponding parent enamides **19** upon reductive cleavage with Na/NH_3.

We also tested the activity of several other reagents for catalyzing cyclizations of type **23** → **27** (R = Bn). As in the case with simple acetylenic amides **18** (*cf.* Scheme 4), no cyclization was observed with benzylamides **23** employing various Pd(II) catalysts under conditions that did not cause concomitant decomposition. In addition, little effect was observed with numerous base catalysts that have previously been employed for related carbamate cyclizations.[13] However, we found it interesting that the reagent system $LiAl(NHBn)_4$ (**31**), prepared *in situ* from $LiAlH_4$ and $BnNH_2$,[18] was highly effective in pro-

(12) Amine cyclizations: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. (b) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812 and references cited therein. (c) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459.

(13) Carbamate cyclizations: Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887.

(14) Acid cyclizations: (a) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385. (b) Marder, T. B.; Chan, D. M.-T.; Fultz, W. C.; Calabrese, J. C.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1885. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976 and references cited therein. (d) Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624.

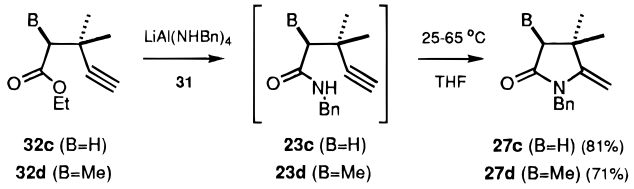
(15) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849.

(16) (a) Klei, E.; Teuben, J. H. *J. Organomet. Chem.* **1981**, *222*, 79. (b) Brix, H.; Beck, W. *J. Organomet. Chem.* **1982**, *234*, 151. (c) Casey, C. P.; Miles, W. H.; Fagan, P. J.; Haller, K. J. *Organometallics* **1985**, *4*, 559. (d) Wong, A.; Pawlick, R. V.; Thomas, C. G.; Leon, D. R.; Liu, L. K. *Organometallics* **1991**, *10*, 530. (e) Adams, H.; Bailey, N. A.; Gauntlett, J. T.; Harkin, I. M.; Winter, M. J.; Woodward, S. *J. Chem. Soc., Dalton Trans.* **1991**, 1117. (f) Hneihen, A. S.; Fermin, M. C.; Mass, J. J.; Bruno, J. W. *J. Organomet. Chem.* **1992**, *429*, 33.

(17) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1991. (b) Watteraon, A. C., Jr.; Shama, S. A. *J. Org. Chem.* **1975**, *40*, 19.

moting cyclization. Reagent **31** has found considerable utility for the conversion of esters and lactones to benzylamides,[18] and in the present case it provides a convenient means for the direct transformation of β-acetylenic esters to cyclic enamides. For example, acetylenic amide **23c** afforded an 81% yield of enamide **27c** after warming for 2 h at 65 °C with 1 equiv of **31** (Scheme 6).

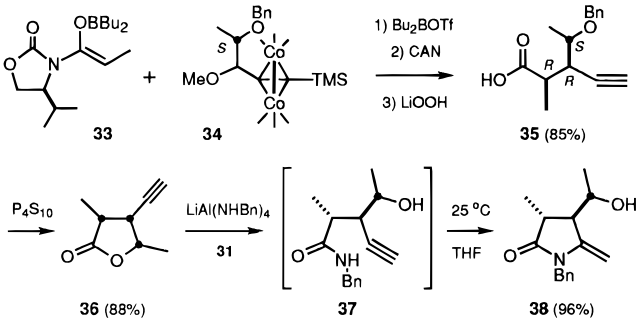
Scheme 6



In similar fashion, acetylenic ester **32d** gave a 71% yield of enamide **27d** after 3 h at 65 °C (2 equiv of **31**; 5% of recovered acetylenic amide **23d** by NMR). It is important to note that no cyclization of intermediate amides **23c**,**d** was observed in the absence of excess **31** or with other reagents known to convert esters to amides.[19]

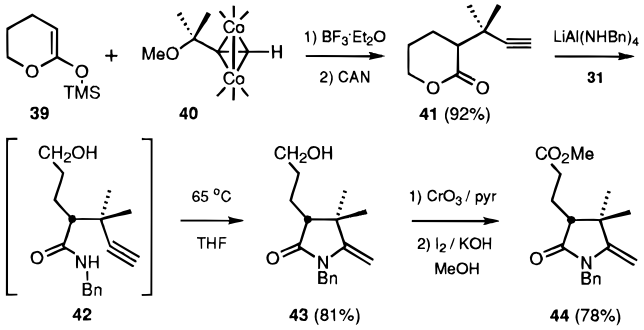
This methodology was first exploited in a highly efficient synthesis of enantiomerically pure enamide **38**, making use of the Nicholas−Schreiber methodology for the synthesis of acetylenic acid **35** (Scheme 7).[4,5] Thus, condensation of Evans' enolate **33** with cobalt complex **34** provided an 85% overall yield of **35** as a single enantiomer, with *syn*-selectivity >98%.[4,20a] Acid **35** was then converted in two steps to enamide **38** by initial deprotection and lactonization to afford lactone **36** (P_4S_{10}, 88%),[20b] which upon treatment with 2 equiv of **31** at 25 °C gave a 96% yield of **38**.[20c] In this case, transformation of intermediate acetylenic amide **37** to enamide **38** was rapid even at 0 °C.

Scheme 7



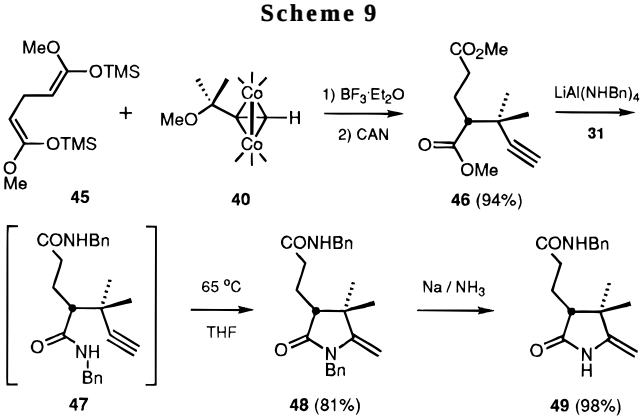
Finally, we have utilized this methodology in two syntheses of cyclic enamides, which are potential ring-c precursors for cobyric acid (**7**) and related corrins. The first of these began with silyl enol ether **39**, which gave a 92% yield of Nicholas adduct **41** upon $BF_3{\cdot}Et_2O$-catalyzed condensation with cobalt complex **40**, followed by oxidative removal of cobalt (CAN) (Scheme 8).[4,5] Interestingly, we observed no competing elimination of MeOH from **40**, a pathway that is frequently a problem with Nicholas condensations involving tertiary carbocations.[4] Adduct **41**, in turn, was converted in a single step to enamide alcohol **43** by initial ring opening with excess $LiAl(NHBn)_4$ (**31**),[18] followed by cyclization of the resultant acetylenic amide **42** at 65 °C (THF; 81% yield). Although it was possible to isolate intermediate **42** in this transformation, it proved to be advantageous to carry out the cyclization *in situ*. Enamide alcohol **43** then gave a 78% yield of methyl ester **44** upon oxidation first with CrO_3/pyridine,[21] followed by I_2 in methanolic KOH.[22] The attractiveness of this approach resides in the ready availability of both **39** and **40**,[4,5] each of which was prepared in a single step from commercially available starting materials. In addition, yields throughout the synthesis are uniformly high.

Scheme 8



An even more direct synthesis of a ring-c enamide was realized beginning with the bis-silyl enol ether **45**, itself readily derived from dimethyl glutarate (Scheme 9).[23] Thus, condensation of **45** with cobalt complex **40** afforded a 94% yield of Nicholas adduct **46** (*vide supra*),[4,5] which was converted in a single step to benzyl-protected enamide **48** by reaction at 65 °C with excess $LiAl(NHBn)_4$ (**31**) (81% yield). As in the case with **42** above (*cf.* Scheme 8), it proved unnecessary to isolate intermediate acetylenic bis-amide **47**, although **47** could be obtained admixed with **48** upon reaction at lower temperatures (25 °C). Finally, we were pleased to find that the enamide benzyl protecting group in **48** could be selectively cleaved with Na/NH_3, affording the parent enamide **49** in virtually quantitative yield.

Scheme 9



Summary

In this paper we described three procedures for converting acetylenic amides of general structure **11** to cyclic

(18) Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.

(19) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(20) (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (b) We are grateful to Dr. Robert DeSimone for initially carrying out this reaciton. (c) We are grateful to Dr. Wanjun Zheng for initially carrying out this reaction.

(21) Ratcliffe, R.; Rodenhurst, R. *J. Org. Chem.* **1970**, *35*, 4000 and references cited therein.

(22) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.

(23) Wallace, I. H. M.; Chan, T. H. *Tetrahedron* **1983**, *39*, 847.

enamides of type **1**: (1) Palladium-catalyzed cyclization in the presence of CO and MeOH, which affords N-unsubstituted enamide esters **21** in moderate to high yields; (2) TBAF-catalyzed cyclization, which gives N-substituted enamides **27**−**30** in excellent yields and at a greatly enhanced rate relative to unsubstituted examples; and (3) $LiAl(NHBn)_4$-catalyzed cyclization of benzylamides, which among other examples was employed in the synthesis of the enantiomerically pure enamide **38** and in syntheses of the potential vitamin B_{12} precursors **44** and **49**. With suitable modification, we believe that the methodology described in this paper might be applied to the synthesis of a wide range of cyclic enamides in enantiomerically pure form, including those of a type useful for the synthesis of biologically important chlorins, isobacteriochlorins, and corrins. Experiments in this direction are currently in progress.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at either 300 or 400 MHz and are expressed as ppm downfield from tetramethysilane.

2,2-Dimethyl-4-pentynamide (18b). A solution of 6.0 g (48.0 mmol) of 2,2-dimethyl-4-pentynoic acid (**17b**)[9b] in 150 mL of anhydrous THF was cooled to 0 °C and was treated in dropwise fashion, with vigorous stirring, with 4.82 g (48.0 mmol, 1.0 equiv) of triethylamine, followed by 6.5 g (48.0 mmol, 1.0 equiv) of isobutyl chloroformate (IBCF). After addition was complete, the resulting suspension was stirred at 0 °C for 30 min before cooling to −78 °C. The reaction was then treated with 5.0 mL of condensed NH_3, and stirring was continued at −78 °C for 1 h and then at ambient temperature for an additional 11 h (NH_3 was allowed to evaporate). At the end of this period the resulting mixture was diluted with 40 mL of brine and extracted with 3 × 30 mL of EtOAc. The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (silica gel, 50% EtOAc/hexanes) to afford 5.6 g (93%) of **18b** as a white solid: mp 85−86 °C; R_f 0.52 (silica gel, 75% EtOAc/hexanes; $KMnO_4$ indicator); IR (KBr) 3402, 3282, 3205, 2976, 2116, 1650, 1619 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.04 (s, 1H), 2.41 (s, 2H), 5.4 (br, 1H), 5.8 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.61, 30.29, 42.22, 71.62, 81.83, 179.65. Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.27; H, 8.86; N, 11.23.

3,3-Dimethyl-4-pentynamide (18c). This material was prepared in 77% yield from 3.0 g (23.8 mmol) of 3,3-dimethyl-4-pentynoic acid (**17c**)[9c] following a procedure identical to that described above (*cf.* **18b**). Chromatography (silica gel, 50% EtOAc/hexanes) afforded 2.3 g (77%) of **18c** as a white solid: mp 56−57 °C; R_f 0.11 (silica gel, 10% EtOAc/hexanes; $KMnO_4$ indicator); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.28 (s, 1H), 2.38 (s, 2H), 5.7 (br, 1H), 6.2 (br, 1H). Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.93; H, 8.92; N, 11.13.

2,3,3-Trimethyl-4-pentynamide (18d). This material was prepared in 93% yield from 1.0 g (7.1 mmol) of 2,3,3-trimethyl-4-pentynoic acid (**17d**)[9d] following a procedure identical to that described above (*cf.* **18b**). Chromatography (silica gel, 50% EtOAc/hexanes) afforded 921 mg (93%) of **18d** as a white solid: mp 63−64 °C; R_f 0.35 (silica gel, 50% EtOAc/hexanes; $KMnO_4$ indicator); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 2.23−2.32 (m, 2H), 5.40 (br, 1H), 6.10 (br, 1H). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.96; H, 9.44; N, 10.13.

4,4-Dimethyl-5-methylene-2-pyrrolidinone (19c). Method A. Decarboxylation of Acid (*Z*)-22c. A total of 31 mg (0.18 mmol) of acid (*Z*)-**22c** (mp 141 °C) was heated under nitrogen in an oil bath maintained at 180 °C for a period of 3 min, at which point gas evolution ceased. Upon cooling there was obtained 22 mg (99%) of pyrrolidinone **19c** as a glassy yellow solid. Recrystallization from pentane afforded **19c** as an unstable yellow solid, mp 72−73 °C, identical in all respects with authentic **19c** prepared following the method of Dillard and Easton (mixed mp 72−73 °C):[24a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.33 (s, 2H), 4.09 (d, J = 1.9 Hz, 1H), 4.29 (d, J = 1.9 Hz, 1H), 8.40 (br, 1H).

Method B. Debenzylation of 27c. Approximately 5−10 mL of liquid NH_3 was distilled from Na metal through a glass tube into a flask containing 123 mg (0.57 mmol) of pyrrolidinone **27c** and equipped with a dry ice/acetone condenser. The reaction mixture was then treated with approximately 131 mg (5.7 mmol, 10 equiv) of Na metal to give a dark blue solution. This solution was maintained at −33 °C for 3 h (reflux) and was then carefully quenched by slow addition of 786 mg (5.7 mmol, 10 equiv) of triethylamine hydrochloride to produce a thick white suspension. The suspension was vigorously mixed to ensure complete quenching of the Na (**Warning**: as with all Na reductions, possible fire hazard). The NH_3 was then allowed to evaporate at rt, and the residue was partitioned between 10 mL of EtOAc and 5 mL of H_2O. The layers were separated, and the aqueous layer was extracted with an additional 2 × 10 mL of EtOAc. The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$, and concentrated to give 62 mg (87%) of **19c** as a white crystalline solid, which rapidly turned yellow on standing at rt. The material thus obtained was identical to **22c** prepared using method A above and also to an authentic sample.[24a] This compound is very unstable and decomposes even during storage at low temperatures.

3,4,4-Trimethyl-5-methylene-2-pyrrolidinone (19d). Method A. Decarboxylation of Acid (*Z*)-22d. This material was prepared in 97% yield from 8.2 mg (0.048 mmol) of acid (*Z*)-**22d** following method A described above (*cf.* **19c**): glassy yellow solid; R_f 0.24 (silica gel, 30% EtOAc/hexanes); MS *m*/*z* 139 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.25 (s, 3H), 2.34 (q, J = 7.4 Hz, 1H), 4.12 (d, J = 1.4 Hz, 1H), 4.28 (d, J = 1.6 Hz, 1H), 7.88 (br, 1H); IR ($CDCl_3$) 3217, 2963, 1711, 1672 cm^{-1}; exact mass calcd for $C_8H_{13}NO$ 139.0997, found 139.0996.

Method B. Debenzylation of 27d. Alternatively, **19d** was prepared in 92% yield from 84 mg (0.37 mmol, 1 equiv) of enamide **27d**, 84 mg (3.7 mmol, 10 equiv) of Na metal, and 10 mL of liquid NH_3 following method B described above (*cf.* **19c**). Workup afforded 47 mg (92%) of **19d** as a white crystalline solid, which rapidly turned yellow on standing.

3,3-Dimethyl-5-methylene-2-pyrrolidinone (19b).[24b] This material was prepared in 82% yield from 86 mg (0.40 mmol) of pyrrolidinone **27b**, 92 mg (4.0 mmol, 10 equiv) of Na metal, and 10 mL of liquid NH_3 following method B described above (*cf.* **19c**). Workup afforded 41 mg (82%) of **19b** as a white crystalline solid, which rapidly turned yellow on standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 6H), 2.56 (s, 2H), 4.11 (br s, 1H), 4.34 (d, J = 1.4 Hz, 1H), 7.80 (br, 1H); exact mass calcd for $C_7H_{11}NO$ 125.0841, found 125.0839.

5-[(Methoxycarbonyl)methylidene]-2-pyrrolidinone (21a).[24c,d] A mixture consisting of 3.7 g (38.0 mmol) of acetylenic amide **18a**, 674 mg (3.8 mmol, 0.1 equiv) of $PdCl_2$, and 20.6 g (152 mmol, 4.0 equiv) of $CuCl_2$ in 300 mL of MeOH was stirred at rt under an atmosphere of CO. After 2 h the color of the reaction mixture had changed from green to black, and after stirring for a total of 3 h the reaction was neutralized by careful addition of powdered $NaHCO_3$. The resulting light green suspension was then filtered with vacuum through Celite and concentrated under reduced pressure. The residue was adsorbed onto silica gel and chromatographed (silica gel, 30% EtOAc/hexanes) to afford 2.1 g (36%) of (*Z*)-**21a** as a colorless solid:[24c,d] R_f 0.41 (silica gel, 40:59:1 EtOAc/hexanes/AcOH); MS *m*/*z* 137 (M^+); IR (KBr) 3347, 2954, 1738, 1689, 1643, 1438, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50−2.60 (m, 2H), 2.85−2.94 (m, 2H), 3.69 (s, 3H), 5.00 (s, 1H), 9.85

(24) (a) Easton, N., R.; Dillard, R. D. *J. Org. Chem.* **1962**, *27*, 3602. (b) Stevens, R. V.; Christensen, C. G.; Edmonson, W. L.; Kaplan, M.; Reid, E. B.; Wentland, M. P. *J. Am. Chem. Soc.* **1971**, *93*, 6629. (c) Gossauer, A.; Hinze, R.-P.; Zilch, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 418. (d) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079.

(br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 27.5, 50.9, 89.5, 157.5, 168.2, 177.3. Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.27; H, 5.87; N, 8.96. Also isolated was 1.5 g (25%) of (*E*)-**21a** as a yellow amorphous powder:[24d] R_f 0.35 (silica gel, 40:59:1 EtOAc/hexanes/AcOH); MS *m*/*z* 137 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50−2.62 (m, 2H), 3.22−3.35 (m, 2H), 3.72 (s, 3H), 5.35 (s, 1H), 7.65 (br, 1H).

5-[(Methoxycarbonyl)methylidene]-3,3-dimethyl-2pyrrolidinone (21b). This material was prepared in 51% yield from 3.0 g (24.0 mmol, 1.0 equiv) of acetylenic amide **18b**, 339 mg (1.9 mmol, 0.08 equiv) of $PdCl_2$, and 9.72 g (72.0 mmol, 3.0 equiv) of $CuCl_2$ in 300 mL of MeOH following a procedure identical to that described above (*cf.* **21a**). Chromatography (silica gel, 50% EtOAc/hexanes) afforded 2.24 g (51%) of **21b** as a 10:1 *Z*:*E* mixture. (*E*)-**21b**: mp 166−168 °C; R_f 0.31 (silica gel, 75% hexanes/EtOAc); MS *m*/*z* 183 (M^+); IR (KBr) 3182, 2975, 1710, 1646, 1136 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 6H), 3.10 (s, 2H), 3.67 (s, 3H), 5.37 (s, 1H), 8.21 (br, 1H). (*Z*)-**21b**: mp 62−63 °C; R_f 0.21 (silica gel, 75% hexanes/EtOAc); MS *m*/*z* 183 (M^+); IR (KBr) 3350, 2965, 1748, 1688, 1641, 1154, 1137 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 6H), 2.67 (s, 2H), 3.67 (s, 3H), 4.96 (s, 1H), 9.6 (br, 1H). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.85; H, 7.15; N, 7.53.

(*Z*)-5-[(Methoxycarbonyl)methylidene]-4,4-dimethyl-2-pyrrolidinone ((*Z*)-21c). This material was prepared in 96% yield from 2.0 g (16.0 mmol, 1.0 equiv) of acetylenic amide **18c**, 227 mg (1.28 mmol, 0.08 equiv) of $PdCl_2$, and 8.64 g (64.0 mmol, 4.0 equiv) of $CuCl_2$ in 200 mL of MeOH following a procedure identical to that described above (*cf.* **21a**). Chromatography (silica gel, 50% EtOAc/hexanes) afforded 2.80 g (96%) of (*Z*)-**21c** as a light yellow solid: mp 74−76 °C; R_f 0.82 (silica gel, EtOAc); MS *m*/*z* 183 (M^+); IR (melt) 3345, 2964, 1750, 1684, 1634, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.40 (s, 2H), 3.71 (s, 3H), 4.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 39.2, 43.7, 51.0, 87.3, 167.0, 168.6, 175.2. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.72; H, 7.24; N, 7.41.

(*Z*)-5-[(Methoxycarbonyl)methylidene]-3,4,4-trimethylpyrrolidinone ((*Z*)-21d). This material was prepared in 72% yield from 200 mg (1.43 mmol, 1.0 equiv) of acetylenic amide **18d**, 21 mg (0.12 mmol, 0.08 equiv) of $PdCl_2$, and 388 mg (2.87 mmol, 2.0 equiv) of $CuCl_2$ in 20 mL of MeOH following a procedure identical to that described above (*cf.* **21a**). Chromatography (silica gel, 50% EtOAc/hexanes) afforded 203 mg (72%) of (*Z*)-**21d** as a colorless oil: R_f 0.72 (silica gel, 50% EtOAc/hexanes); IR (neat) 3351, 2966, 1745, 1692, 1633, 1173cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 8 Hz, 3H),1.08 (s, 3H), 1.20 (s, 3H), 2.30 (q, J = 8 Hz, 1H), 3.66 (s, 3H), 5.01 (s, 1H), 9.85 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 24.1, 26.5, 42.5, 45.8, 50.9, 87.4, 166.5, 168.7, 178.1. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.80; H, 7.68; N, 7.04.

(*Z*)-(3*S*,4*S*)-5-[(Methoxycarbonyl)methylidene]-3,4-dimethyl-2-pyrrolidinone ((*Z*)-21f). This material was prepared in 50% yield from 420 mg (3.36 mmol, 1.0 equiv) of acetylenic amide **18f**, 48 mg (0.26 mmol, 0.08 equiv) of $PdCl_2$, and 907 mg (6.72 mmol, 2.0 equiv) of $CuCl_2$ in 25 mL of MeOH following a procedure identical to that described above (*cf.* **21a**). Chromatography (silica gel, 10% EtOAc/hexanes) afforded 305 mg (50%) of (*Z*)-**21f** as a colorless oil: R_f 0.61 (silica gel, 50% hexanes/EtOAc); MS *m*/*z* 183 (M^+); IR (neat) 3351, 2969, 1748, 1688, 1643, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 10 Hz, 3H), 1.30 (d, J = 8 Hz, 3H), 2.23 (m, 1H), 2.65 (m, 1H), 3.70 (s, 3H). 5.01 (s, 1H), 9.75 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 17.1, 41.6, 42.4, 50.9, 88.4, 161.2, 168.4, 178.7; $[\alpha]^{25}_D$ = −20.0° (c = 10, MeOH); exact mass calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0896. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.25; H, 7.22; N, 7.59.

(*Z*)-(3*R*,4*R*)-5-[(Methoxycarbonyl)methylidene]-3,4-dimethyl-2-pyrrolidinone ((*Z*)-21e). This material was prepared in 50% yield from acetylenic amide **18e** following a procedure identical to that described above for enantiomer (*Z*)-**21f**: $[\alpha]^{25}_D$ = +22.2° (c = 10, MeOH), spectral data identical to (*Z*)-**21f**.

(*Z*)-5-(Carboxymethylidene)-4,4-dimethyl-2-pyrrolidinone ((*Z*)-22c). A solution of 183 mg (1.0 mmol, 1.0 equiv) of ester (*Z*)-**21c** in 15 mL of CCl_4 was treated with 500 mg (2.5 mmol, 2.5 equiv) of trimethylsilyl iodide (TMSI), and the resulting mixture was stirred at 50 °C for 24 h. By the end of this time the reaction had turned dark red and contained a black precipitate. The reaction was then treated with 5 mL of 0.5 N NaOH and 5 mL of CH_2Cl_2, and the resulting yellow suspension was extracted with 3 × 5 mL of 0.5 N NaOH. The aqueous extracts were then carefully acidified to pH 4 with 5% HCl and back-extracted with 3 × 5 mL of CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford 152 mg (90%) of (*Z*)-**22c** as a white solid: mp 141 °C (with decarboxylation); IR (KBr) 3357, 1718, 1701, 1595, 1227cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 6H), 2.40 (s, 2H), 5.02 (s, 1H) 9.82 (br s, 1H). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.76; H, 6.54; N, 8.21.

(*Z*)-5-(Carboxymethylidene)-3,4,4-trimethyl-2-pyrrolidinone ((*Z*)-22d). A solution consisting of 100 mg (0.51 mmol, 1.0 equiv) of ester (*Z*)-**21d**, 6 mL of 1.0 M aqueous LiOH, and 4 mL of MeOH was heated at reflux for a period of 30 min. The reaction mixture was then concentrated to about 5 mL under reduced pressure, cooled to 0 °C, and carefully acidified to pH 2 with 10% HCl. The resulting solution was extracted with 4 × 5 mL of EtOAc, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (silica gel, EtOAc) then afforded 86 mg (93%) of acid (*Z*)-**22d** as a white solid: mp 126 °C (from EtOAc/hexanes; melts with decarboxylation); IR (KBr) 3363, 2966, 1753, 1673, 1643, 1595, 1194 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 6H), 1.14 (s, 3H) 2.35 (m, 1H), 5.02 (s, 1H) 9.70 (br s, 1H).

General Procedures for the Preparation of Acetylenic Amides 23−26. Method A. A solution of 10.8 mmol (1.0 equiv) of the appropriate acetylenic acid **17** in 50 mL of anhydrous THF was cooled to 0 °C under an atmosphere of argon and was treated in dropwise fashion, with vigorous stirring, with 11.8 mmol (1.1 equiv) of NEt_3, followed by 11.8 mmol (1.1 equiv) of isobutyl chloroformate (IBCF). The resulting white suspension was stirred at 0 °C for an additional 1 h and was then cooled to −78 °C. The resulting mixed anhydride was then treated in dropwise fashion, and with vigorous stirring, with 13.0 mmol (1.2 equiv) of the appropriate amine, and the reaction was allowed to warm slowly to rt. Stirring was continued at rt for an additional 16 h, and the reaction was then partitioned between 50 mL of brine and 50 mL of EtOAc. The layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to an oil. The crude product was purified by flash chromatography to afford acetylenic amides **23**−**26**.

Method B. A total of 2.18 mmol (1.0 equiv) of the appropriate acetylenic acid **17** was covered with 34.4 mmol (16.0 equiv) of oxalyl chloride, and the mixture was heated at 55 °C for a period of 3.5 h to afford a yellow solution. The reaction was then cooled to rt and concentrated under reduced pressure to remove excess oxalyl chloride. The crude acid chloride was dissolved in 2.0 mL of anhydrous CH_2Cl_2 and transferred by syringe to a cooled (0 °C), well-stirred solution of 10.9 mmol (5.0 equiv) of the appropriate amine in 1.0 mL of CH_2Cl_2. The resulting suspension was allowed to warm slowly to rt, and stirring was continued for an additional 16 h. The reaction was then partitioned between 10 mL of brine and 20 mL of CH_2Cl_2. The layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to an oil. The crude product was purified by flash chromatography to afford acetylenic amides **23**−**26**.

***N*-Benzyl-4-pentynamide (23a).** This material was prepared in 88% yield from 237 mg (2.41 mmol) of acid **17a** and 0.32 mL (2.89 mmol, 1.2 equiv) of benzylamine using method A described above. Purification by chromatography (silica gel, 50% EtOAc/hexanes, R_f 0.33) gave 398 mg of **23a** as a white crystalline solid: mp 69−70 °C (EtOAc/hexanes); IR ($CDCl_3$) 3295, 1631, 1539 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (t, J = 2.5 Hz, 1H), 2.42−2.48 (m, 2H), 2.54−2.62 (m, 2H), 4.48 (d, J = 5.7 Hz, 2H), 5.90 (br, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 35.5, 43.8, 69.6, 83.2, 127.7, 128.0,

128.8, 138.3, 171.0. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.92; H, 7.05; N, 7.41.

***N*-Benzyl-2,2-dimethyl-4-pentynamide (23b).** This material was prepared in 70% yield from 625 mg (4.95 mmol) of acid **17b** and 0.65 mL (5.94 mmol, 1.2 equiv) of benzylamine using method A described above. Purification by chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.33) gave 746 mg of **23b** as a white solid: mp 69−71 °C (EtOAc/hexanes); IR ($CDCl_3$) 3296, 2964, 1638, 1533; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H), 2.04 (t, J = 2 Hz, 1H), 2.48 (d, J = 2 Hz, 2H), 4.48 (d, J = 5.7 Hz, 2H), 6.12 (br, 1H), 7.27−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 30.2, 42.0, 43.9, 71.2, 81.6, 127.6, 127.9, 128.9, 138.6, 176.3. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.08; H, 7.94; N, 6.48.

***N*-Benzyl-3,3-dimethyl-4-pentynamide (23c).** This material was prepared in 87% yield from 338 mg (2.68 mmol) of acid **17c** and 0.35 mL (3.22 mmol, 1.2 equiv) of benzylamine using method A described above. Purification by chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.27) gave 503 mg of **23c** as a colorless oil: IR ($CDCl_3$) 3295, 2966, 1643, 1543 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.19 (s,1H), 2.39 (s, 2H), 4.49 (d, J = 5.6 Hz, 2H), 6.39 (br, 1H), 7.28−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 30.0, 43.7, 49.6, 69.8, 91.0, 127.5, 127.9, 128.7, 138.4, 170.1; exact mass calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1311.

***N*-Benzyl-2,3,3-trimethyl-4-pentynamide (23d).** This material was prepared in 83% yield from 267 mg (1.9 mmol) of acid **17d** and 1.04 mL (9.5 mmol, 5 equiv) of benzylamine using method B described above. Purification by chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.33) gave 364 mg of **23d** as a colorless solid: mp 83−84 °C (EtOAc/hexanes); IR (CH_2Cl_2) 3287, 1635, 1535 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.30 (d, J = 7.2 Hz, 3H), 1.32 (s, 3H), 2.21 (s, 1H), 2.29 (q, J = 7.2 Hz, 1H), 4.48 (d, J = 5.5 Hz, 2H), 6.30 (br, 1H), 7.29−7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 27.6, 27.9, 33.6, 43.7, 51.5, 70.8, 90.2, 127.6, 128.0, 128.8, 138.6, 174.2. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40; H, 8.31; N, 6.02.

***N*-Benzyl-2(*R*),3(*R*)-dimethyl-4-pentynamide (23e).** This material was prepared in 81% yield from 287 mg (2.27 mmol) of acid **17e** and 0.30 mL (2.72 mmol, 1.2 equiv) of benzylamine using method A described above. Purification by chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.25) gave 394 mg of **23f** as a colorless, crystalline solid: mp 64−65 °C (EtOAc/hexanes); IR ($CDCl_3$) 3288, 1643, 1549 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 2.10 (d, J = 2.4 Hz, 1H), 2.35 (m, 1H), 2.78 (m, 1H), 4.40−4.56 (m, 2H), 6.06 (br, 1H), 7.24−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 18.2, 29.3, 43.8, 46.7, 70.6, 87.2, 127.7, 128.1, 128.9, 138.6, 174.4; $[\alpha]^{26}_D$ = +12.69° (c = 0.26, CH_2Cl_2). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.22; H, 7.98; N, 6.45.

***N*-Benzyl-2(*S*),3(*S*)-dimethyl-4-pentynamide (23f).** This material was prepared in 65% yield from 372 mg (2.95 mmol) of acid **17f** and 0.39 mL (3.54 mmol, 1.2 equiv) of benzylamine using method A described above. Purification by chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.25) gave 410 mg of **23f** as a colorless solid: mp 64−65 °C (EtOAc/hexanes); spectral data identical to that of **23e**; $[\alpha]^{26}_D$ = −12.44° (c = 0.45, CH_2Cl_2). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.17; H, 8.00; N, 6.46.

***N*-(4-Methoxybenzyl)-2,2-dimethyl-4-pentynamide (24b).** This material was prepared in 62% yield from 213 mg (1.68 mmol) of acid **17b** and 0.26 mL (2.02 mmol, 1.2 equiv) of *p*-methoxybenzylamine using method A described above. Purification by chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.27) gave 257 mg of **24b** as a white solid: mp 75−77 °C (EtOAc/hexanes); IR ($CDCl_3$) 3300, 2964, 1641, 1512, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6H), 2.03 (t, J = 2.7 Hz, 1H), 2.46 (d, J = 2.7 Hz, 2H), 3.80 (s, 3H), 4.40 (d, J = 5.5 Hz, 2H), 6.05 (br, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 30.2, 41.9, 43.4, 55.5, 71.2, 81.6, 114.3, 129.3, 130.7, 159.2, 176.3. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 7.83; N, 5.65.

***N*-(4-Methoxybenzyl)-3,3-dimethyl-4-pentynamide (24c).** This material was prepared in 86% yield from 176 mg (1.39 mmol) of acid **17c** and 0.22 mL (1.67 mmol, 1.2 equiv) of *p*-methoxybenzylamine using method A described above. Purification by chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.22) gave 296 mg of **24c** as a colorless, crystalline solid: mp 55−57 °C; IR ($CDCl_3$) 3295, 2929, 1648, 1543, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 2.19 (s,1H), 2.38 (s, 2H), 3.81 (s, 3H), 4.42 (d, J = 5.5 Hz, 2H), 6.32 (br, 1H), 6.87 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 30.0, 43.1, 49.5, 55.3, 69.7, 91.0, 114.0, 129.1, 130.6, 159.0, 169.9. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.16; H, 7.75; N, 5.59.

***N*-(4-Methoxybenzyl-2,3,3-trimethyl-4-pentynamide (24d).** This material was prepared in 71% yield from 305 mg (2.18 mmol) of acid **17d** and 1.4 mL (10.9 mmol, 5 equiv) of *p*-methoxybenzylamine using method B described above. Purification by chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.34) gave 399 mg of **24d** as a colorless solid: mp 70−72 °C; IR ($CDCl_3$) 3293, 2970, 1644, 1512, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 2.19 (s, 1H), 2.26 (q, J = 7.2 Hz, 1H), 3.81 (s, 3H), 4.40 (d, J = 5.5 Hz, 2H), 6.30 (br, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 26.8, 27.6, 33.4, 42.7, 50.5, 55.1, 70.2, 90.1, 113.9, 129.0, 130.6, 158.8, 173.9. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.19; H, 8.20; N, 5.43.

***N*-(3,4-Dimethoxybenzyl)-2,2-dimethyl-4-pentynamide (25b).** This material was prepared in 60% yield from 186 mg (1.47 mmol) of acid **17b** and 0.27 mL (1.76 mmol, 1.2 equiv) of 3,4-dimethoxybenzylamine using method A described above. Purification by chromatography (silica gel, 40% EtOAc/hexanes, R_f 0.27) gave 242 mg of **25b** as an off-white solid: mp 98−99 °C (EtOAc/hexanes); IR ($CDCl_3$) 3290, 2964, 1641, 1516, 1264 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 6H), 2.03 (t, J = 2.6 Hz, 1H), 2.47 (d, J = 2.6 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.40 (d, J = 5.6 Hz, 2H), 6.07 (br, 1H), 6.80−6.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 30.2, 42.0, 43.8, 56.1, 56.2, 71.2, 81.7, 111.4, 111.5, 120.2, 131.3, 148.7, 149.4, 176.3. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.67; N, 5.09. Found: C, 69.71; H, 7.70; N, 5.06.

***N*-(3,4-Dimethoxybenzyl)-3,3-dimethyl-4-pentynamide (25c).** This material was prepared in 67% yield from 211 mg (1.67 mmol) of acid **17c** and 0.30 mL (2.00 mmol, 1.2 equiv) of 3,4-dimethoxybenzylamine using method A described above. Purification by chromatography (silica gel, 40% EtOAc/hexanes, R_f 0.14 in 30% EtOAc/hexanes) gave 310 mg of **25c** as a white solid: mp 75−77 °C; IR ($CDCl_3$) 3291, 2968, 1646, 1516, 1264 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 2.19 (s, 1H), 2.38 (s, 2H), 3.87 (s, 6H), 4.42 (d, J = 5.6 Hz, 2H), 6.35 (br, 1H), 6.80−6.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 29.9, 43.2, 49.3, 55.76, 55.81, 69.5, 90.8, 111.1, 119.9, 131.0, 148.2, 149.0, 169.9. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.72; H, 7.73; N, 5.04.

***N*-(3,4-Dimethoxybenzyl)-2,3,3-trimethyl-4-pentynamide (25d).** This material was prepared in 77% yield from 252 mg (1.80 mmol) of acid **17d** and 1.4 mL (9.0 mmol, 5 equiv) of 3,4-dimethoxybenzylamine using method B described above. Purification by chromatography (silica gel, 40% EtOAc/hexanes, R_f 0.21 in 30% EtOAc/hexanes) gave 400 mg of **25d** as a white solid: mp 104−105 °C (EtOAc/hexanes); IR ($CDCl_3$) 3294, 2972, 1646, 1514, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (d, J = 7.1 Hz, 3H), 1.34 (s, 3H), 2.20 (s, 1H), 2.28 (q, J = 7.1 Hz, 1H), 3.87 (s, 6H), 4.39−4.43 (m, 2H), 6.28 (br, 1H), 6.80−6.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 27.4, 27.8, 33.6, 43.4, 51.3, 56.0, 56.1, 70.7, 90.2, 111.4, 120.1, 131.3, 148.5, 149.3, 174.0. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.66; H, 8.07; N, 4.89.

3,3-Dimethyl-4-pentynoic Acid, *N*′-Methyl-*N*′-(methoxycarbonyl)hydrazide (26c). This material was prepared in 79% yield from 369 mg (2.92 mmol) of acid **17c** and a solution of 366 mg (3.51 mmol, 1.2 equiv) of 1-(methoxycarbonyl)-1-methylhydrazine[25] in 2 mL of anhydrous THF using

(25) Wadsworth, W. S. *J. Org. Chem.* **1969**, *34*, 2994.

method A described above. Purification by chromatography (silica gel, 50% EtOAc/hexanes, R_f 0.45 in 70% EtOAc/hexanes) gave 491 mg of **26c** as a white crystalline solid: mp 79−81 °C (EtOAc/hexanes); IR ($CDCl_3$) 3274, 2964, 1715, 1676, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 6H), 2.30 (s, 1H), 2.39 (s, 2H), 3.19 (s, 3H), 3.73 (br s, 3H), 7.94 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 30.1, 37.9, 47.5, 53.4, 69.9, 90.7, 156.9, 169.0. Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.51; H, 7.65; N, 13.13.

***N*-Benzyl-5-methylene-2-pyrrolidinone (27a).** A solution of 107 mg (0.57 mmol, 1.0 equiv) of acetylenic amide **23a** in 5.7 mL of anhydrous THF was treated in dropwise fashion, and with vigorous stirring, with a solution of 0.57 mL (0.57 mmol, 1.0 equiv) of freshly prepared 1.0 M tetra-*n*-butylammonium fluoride (TBAF) in THF. After addition was complete, the reaction mixture was heated at reflux under an argon atmosphere for a period of 8.5 h. At the end of this period the reaction mixture was cooled, concentrated under reduced pressure (bath temperature 25 °C), and chromatographed (silica gel, 20% EtOAc/hexanes, R_f 0.37 in 30% EtOAc/hexanes) to give 90 mg (84%) of **27a** as a colorless oil: IR (CH_2Cl_2) 1719, 1664, 1393 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52−2.65 (m, 2H), 2.67−2.80 (m, 2H), 4.12 (d, J = 1.8 Hz, 1H), 4.19 (d, J = 1.8 Hz, 1H), 4.68 (s, 2H), 7.20−7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 29.2, 43.8, 85.5, 127.4, 127.5, 128.7, 136.2, 146.4, 176.1; exact mass calcd for $C_{12}H_{13}NO$ 187.0997, found 187.0994.

***N*-Benzyl-3,3-dimethyl-5-methylene-2-pyrrolidinone (27b).** This material was prepared in 100% yield from 127 mg (0.59 mmol) of acetylenic amide **23b** in 5.9 mL of anhydrous THF and 0.59 mL (0.59 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.5 h). Chromatography (silica gel, 10% EtOAc/hexanes, R_f 0.25) afforded 133 mg (100%) of **27b** as a colorless oil that crystallized upon standing: mp 33−36 °C; IR (CH_2Cl_2) 3413, 2954, 1719, 1666, 1396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.56 (br s, 2H), 4.11 (d, J = 2 Hz, 1H), 4.20 (d, J = 2 Hz, 1H), 4.67 (s, 2H), 7.19−7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 40.0, 40.6, 43.8, 85.8, 127.2, 127.4, 128.7, 136.5, 144.1, 181.2; exact mass calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1311.

***N*-Benzyl-4,4-dimethyl-5-methylene-2-pyrrolidinone (27c). Method A. Cyclization with TBAF.** This material was prepared in 98% yield from 333 mg (1.55 mmol) of acetylenic amide **23c** in 15 mL of anhydrous THF and 1.55 mL (1.55 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 2.5 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.42) afforded 328 mg (98%) of **27c** as a pale yellow oil: IR ($CDCl_3$) 2966, 1719, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.44 (s, 2H), 4.11 (d, J = 2 Hz, 1H), 4.14 (d, J = 2 Hz, 1H), 4.69 (s, 2H), 7.20−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 36.5, 43.7, 45.0, 83.6, 127.1, 127.3, 128.6, 136.2, 156.7, 173.9; exact mass calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1311.

Method B. Cyclization with Reagent 31. A solution of 111 mg (0.52 mmol) of acetylenic amide **23c** in 2 mL of anhydrous THF was added to a solution of 0.52 mmol (1 equiv) of reagent **31**, prepared *in situ* from 20 mg (0.52 mmol, 1.0 equiv) of $LiAlH_4$, 0.28 mL (2.58 mmol, 5.0 equiv) of benzylamine, and 2 mL of anhydrous THF following the general procedure of Solladié-Cavallo.[18] After addition was complete, the reaction was heated at reflux for a period of 2 h, cooled to rt, and carefully quenched by sequential addition of 1 mL of H_2O, 1 mL of 2 N NaOH, and 3 mL of H_2O. The mixture was stirred at rt until a precipitate formed and was then extracted with 2 × 10 mL of CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. Chromatography (silica gel, 20% EtOAc/hexanes) afforded 90 mg of **27c** (81%) as a pale yellow oil, identical to that obtained using method A above.

***N*-Benzyl-3,4,4-trimethyl-5-methylene-2-pyrrolidinone (27d). Method A. Cyclization with TBAF.** This material was prepared in 99% yield from 234 mg (1.0 mmol) of acetylenic amide **23d** in 10 mL of anhydrous THF and 1.0 mL (1.0 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.5 h). Chromatography (silica gel, 15% EtOAc/hexanes) afforded 232 mg (98%) of **27d** as a colorless oil, identical to that obtained using method B below.

Method B. Cyclization with Reagent 31. A solution of 168 mg (1.0 mmol) of acetylenic ester **32d** in 5 mL of anhydrous THF was added to a solution of 2.0 mmol (2.0 equiv) of reagent **31**, prepared *in situ* from 76 mg (2.0 mmol) of $LiAlH_4$, 856 mg (8.0 mmol) of benzylamine, and 5 mL of anhydrous THF following the general procedure of Solladié-Cavallo.[18] After addition was complete, the reaction was heated at reflux for a period of 3 h, cooled to rt, and carefully quenched by sequential addition of 1 mL of H_2O, 1 mL of 2 N NaOH, and 3 mL of H_2O. The mixture was stirred at rt until a precipitate formed and was then extracted with 2 × 10 mL CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.32) afforded 162 mg (71%) of pyrrolidinone **27d** as a light yellow oil: MS m/z 229 (M^+); IR (neat) 2968, 2870, 1720, 1663, 1635, 1395, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.19 (d, J = 7 Hz, 3H), 1.26 (s, 3H), 2.42 (q, J = 7 Hz, 1H), 4.10−4.20 (m, 2H), 4.62 (d, J = 15.4 Hz, 1H), 4.74 (d, J = 15.4 Hz, 1H), 7.20−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 24.4, 27.4, 40.6, 43.9, 47.0, 83.8, 127.4, 127.5, 128.7, 136.6, 156.4, 177.3; exact mass calcd for $C_{15}H_{19}NO$ 229.1466, found 229.1467.

***N*-Benzyl-3(*R*),4(*R*)-dimethyl-5-methylene-2-pyrrolidinone (27e).** This material was prepared in 92% yield from 197 mg (0.92 mmol) of acetylenic amide **23e** in 9.0 mL of anhydrous THF and 0.92 mL (0.92 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.47) afforded 182 mg (92%) of **27e** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 7.2 Hz, 3H), 2.25 (m, 1H), 2.49 (m, 1H), 4.12 (m, 1H), 4.20 (m, 1H), 4.63 (d, J = 15.4 Hz, 1H), 4.72 (d, J = 15.4 Hz, 1H), 7.19−7.36 (m, 5 H); exact mass calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1309.

***N*-Benzyl-3(*S*),4(*S*)-dimethyl-5-methylene-2-pyrrolidinone (27f).** This material was prepared in 93% yield from 215 mg (1.0 mmol) of acetylenic amide **23f** in 10 mL of anhydrous THF and 1.0 mL (1.0 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.47) afforded 201 mg (93%) of **27f** as a colorless oil, with spectral data identical to those of **27e**: exact mass calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1309.

***N*-(4-Methoxybenzyl)-3,3-dimethyl-5-methylene-2-pyrrolidinone (28b).** This material was prepared in 82% yield from 274 mg (1.19 mmol) of acetylenic amide **24b** in 12 mL of anhydrous THF and 1.2 mL (1.2 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.42 in 30% EtOAc/hexanes) afforded 224 mg (82%) of **28b** as a colorless oil: IR ($CDCl_3$) 2961, 1716, 1668, 1514, 1398, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 2.53 (t, J = 1.8 Hz, 2H), 3.79 (s, 3H), 4.10 (d, J = 1.8 Hz, 1H), 4.22 (d, J = 1.8 Hz, 1H), 4.60 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 39.9, 40.6, 43.2, 55.2, 85.6, 114.0, 128.5, 128.6, 144.1, 158.9, 181.0; exact mass calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1417.

***N*-(4-Methoxybenzyl)-4,4-dimethyl-5-methylene-2-pyrrolidinone (28c).** This material was prepared in 100% yield from 175 mg (0.71 mmol) of acetylenic amide **24c** in 7.1 mL of anhydrous THF and 0.71 mL (0.71 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 2.0 h). Chromatography (silica gel, 30% EtOAC/hexanes, R_f 0.42) afforded 175 mg (100%) of **28c** as a colorless oil: IR ($CDCl_3$) 2949, 1716, 1665, 1511 1389 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6H), 2.42 (s, 2H), 3.79 (s, 3H), 4.11 (d, J = 2.3 Hz, 1H), 4.17 (d, J = 2.3 Hz, 1H), 4.61 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.16

(d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 36.6, 43.2, 45.0, 55.2, 83.5, 114.0, 128.4, 128.5, 156.8, 158.9, 173.9; exact mass calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1417.

***N*-(4-Methoxybenzyl)-3,4,4-trimethyl-5-methylene-2-pyrrolidinone (28d).** This material was prepared in 98% yield from 210 mg (0.81 mmol) of acetylenic amide **24d** in 8.1 mL of anhydrous THF and 0.81 mL (0.81 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.39) afforded 206 mg (98%) of **28d** as a colorless oil: IR ($CDCl_3$) 2962, 1716, 1659, 1511, 1395 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.13 (d, J = 7.4 Hz, 3H), 1.20 (s, 3H), 2.34 (q, J = 7.4 Hz, 1H), 3.73 (s, 3H), 4.10 (d, J = 2 Hz, 1H), 4.15 (d, J = 2 Hz, 1H), 4.51 (d, J = 15 Hz, 1H), 4.63 (d, J = 15 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 24.1, 27.1, 40.3, 43.1, 46.7, 55.2, 83.5, 113.9, 128.5, 156.1, 158.9, 176.9; exact mass calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1566.

***N*-(3,4-Dimethoxybenzyl)-3,3-dimethyl-5-methylene-2-pyrrolidinone (29b).** This material was prepared in 89% yield from 67 mg (0.24 mmol) of acetylenic amide **25b** in 4.0 mL of anhydrous THF and 0.24 mL (0.24 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.24) afforded 59 mg (89%) of **29b** as a colorless oil: IR (CH_2Cl_2) 2960, 1715, 1666, 1517, 1398, 1261, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6H), 2.53 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.11 (d, J = 1.5 Hz, 1H), 4.23 (d, J = 1.5 Hz, 1H), 4.60 (s, 2H), 6.72−6.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 40.0, 40.7, 43.6, 55.9, 56.0, 85.7, 110.7, 111.3, 119.7, 129.2, 144.2, 148.5, 149.3, 181.2; exact mass calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1521.

***N*-(3,4-Dimethoxybenzyl)-4,4-dimethyl-5-methylene-2-pyrrolidinone (29c).** This material was prepared in 100% yield from 110 mg (0.40 mmol) of acetylenic amide **25c** in 4.0 mL of anhydrous THF and 0.40 mL (0.40 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.27) afforded 111 mg (100%) of **29c** as a colorless oil: IR ($CDCl_3$) 2959, 1717, 1663, 1515, 1259 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 2.42 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.12 (d, J = 2.3 Hz, 1H), 4.19 (d, J = 2.3 Hz, 1H), 4.62 (s, 2H), 6.75−6.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 36.5, 43.4, 44.9, 55.9, 83.6, 110.5, 111.2, 119.6, 128.8, 148.3, 149.2, 156.7, 173.9; exact mass calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1518.

***N*-(3,4-Dimethoxybenzyl)-3,4,4-trimethyl-5-methylene-2-pyrrolidinone (29d).** This material was prepared in 100% yield from 184 mg (0.64 mmol) of acetylenic amide **25d** in 6.4 mL of anhydrous THF and 0.64 mL (0.64 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 3.0 h). Chromatography (silica gel, 30% EtOAc/hexanes, R_f 0.31) afforded 200 mg (100%) of **29d** as a colorless oil: IR (CH_2Cl_2) 2962, 1716, 1659, 1517, 1459, 1395, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.16 (d, J = 7.3 Hz, 3H), 1.24 (s, 3H), 2.38 (q, J = 7.3 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.14 (d, J = 2.1 Hz, 1H), 4.19 (d, J = 2.1 Hz, 1H), 4.54 (d, J = 15.2 Hz, 1H), 4.67 (d, J = 15.2 Hz, 1H), 6.72−6.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 24.1, 27.2, 40.4, 43.4, 46.8, 55.8, 55.9, 83.6, 110.5, 111.1, 119.7, 129.1, 148.3, 149.2, 156.1, 177.0; exact mass calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1671.

***N*-[*N′*-Methyl-*N′*-(methoxycarbonyl)amino]-4,4-dimethyl-5-methylene-2-pyrrolidinone (30c).** This material was prepared in 90% yield from 115 mg (0.54 mmol) of acetylenic hydrazide **26c** in 5.4 mL of anhydrous THF and 0.54 mL (0.54 mmol, 1.0 equiv) of freshly prepared 1.0 M TBAF/THF, following a procedure identical to that described above for **27a** (heating time 1.0 h). Chromatography (silica gel, 25% EtOAc/hexanes, R_f 0.20) afforded 103 mg (90%) of **30c** as a colorless oil: IR ($CDCl_3$) 2954, 1743, 1719, 1449, 1349 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; mixture of rotomers) δ 1.29−1.35 (br, 6H), 2.34 (s, 2H), 3.19, 3.20 (2s, 3H total), 3.71, 3.81 (2s, 3H total), 4.19 (d, J = 2 Hz, 1H), 4.27 (d, J = 2 Hz, 1H); exact mass calcd for $C_{10}H_{16}N_2O_3$ 215.1310, found 215.1309.

2(*R*),4(*S*)-Dimethyl-3(*R*)-ethynyl-γ-butyrolactone (36). A solution of 95 mg (0.39 mmol, 1.0 equiv) of acetylenic acid **35**[4h] in 3.0 mL of CH_2Cl_2 was treated at rt, with vigorous stirring, with 17.2 mg (0.39 mmol, 1.0 equiv) of P_4S_{10} under an atmosphere of N_2. The reaction mixture was then stirred at rt for 46 h before being diluted with 10 mL of H_2O and extracted with 3 × 6 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 30% acetone/hexanes) to afford 47.3 mg (88%) of lactone **36** as a white solid: mp 55−56 °C (acetone/hexanes); $[\alpha]^{26}_D = -100.0°$ (c = 0.29, EtOAc). Similar yields were obtained for this reaction on gram scales and larger but using 2 equiv) of P_4S_{10}: R_f 0.52 (silica gel, 30% acetone/hexane); IR (CH_2Cl_2) 3053.7, 2986.3, 2305.2, 2253.7, 1774.3, 1421.7, 1265.1, 1181.4, 1054.6, 1014.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 8.5 Hz, 3H), 1.51 (d, J = 5.9 Hz, 3H), 2.31 (d, J = 2.0 Hz, 1H), 2.83 (dq, J = 9.0, 8.5 Hz, 1H), 3.33 (m, 1H), 4.48 (dq, J = 6.0, 5.9 Hz, 1H); MS *m/e* 138 (M^+), 123, 110, 94, 77, 66, 43, 39. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.60; H, 7.33.

***N*-Benzyl-3(*R*)-methyl-4(*R*)-(hydroxyethyl)-5-methylene-2-pyrrolidinone (38).** A solution of 850 mg (6.15 mmol, 1 equiv) of lactone **36** in 3.0 mL of anhydrous THF was added to a solution of 6.15 mmol (1 equiv) of reagent **31**, prepared *in situ* from 246 mg (6.16 mmol, 1 equiv) of $LiAlH_4$, 3.36 mL (30.8 mmol, 5 equiv) of benzylamine, and 5.0 mL of anhydrous THF following the general procedure of Solladié-Cavallo.[18] After addition was complete, the reaction mixture was stirred at rt for 17 h and was then carefully quenched by sequential addition of 0.24 mL of H_2O, 0.24 mL of 10% KOH, and 0.71 mL of H_2O. The mixture was then filtered through Celite and washed with 5 × 3 mL of CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, 50% EtOAc/hexanes, R_f 0.33) to afford 1.45 g (96%) of **38** as colorless crystals: mp 87−89 °C (EtOAc/hexane); $[\alpha]^{26}_D = -14.9°$ (c = 0.35, EtOAc); IR 3607, 1715, 1637 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6 Hz, 3H), 1.33 (d, J = 6 Hz, 3H), 1.85 (m, 1H), 2.45−2.59 (m, 2H), 3.75 (m, 1H), 4.19 (s, 1H), 4.29 (s, 1H), 4.57 (d, J = 16 Hz, 1H), 4.74 (d, J = 16 Hz, 1H), 7.14−7.35 (m, 5H); exact mass calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1414.

3-(1,1-Dimethyl-2-propynyl)tetrahydro-2*H*-pyran-2-one (41). A solution of 3.0 g (7.81 mmol, 1.0 equiv) of cobalt complex **40**[4h] and 2.69 g (15.63 mmol, 2.0 equiv) of silyl enol ether **39**[26] in 50 mL of anhydrous CH_2Cl_2 was cooled to −78 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 2.22 g (15.6 mmol, 2.0 equiv) of BF_3·Et_2O. After addition was complete, the resulting solution was stirred for an additional 30 min at −78 °C and then for 30 min at rt. The reaction was then carefully quenched with 20 mL of pH 7 buffer and extracted with 3 × 10 mL of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (silica gel, 10% EtOAc/hexanes, R_f 0.70) afforded 3.42 g (97%) of the intermediate cobalt-protected Nicholas adduct as a dark oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.50 (s, 3H), 1.70−2.00 (m, 3H), 2.21 (m, 1H), 2.43 (m, 1H), 4.16−4.30 (m, 2H), 6.18 (s, 1H). Anal. Calcd for $C_{16}H_{14}Co_2O_8$: C, 42.50; H, 3.12. Found: C, 42.59; H, 3.18.

A total of 3.42 g (7.56 mmol) of the cobalt-protected Nicholas adduct described above was dissolved in 200 mL of acetone. Ceric ammonium nitrate (CAN) was added in small portions over 20 min, with vigorous stirring, until gas evolution ceased. The solution was then concentrated under reduced pressure, and the resulting red oil was diluted with 50 mL of H_2O. This now orange-colored solution was extracted with 6 × 20 mL of Et_2O, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Vacuum distillation of the residue afforded 1.15 g (92%) of lactone **41** as a colorless oil: $bp_{0.75mm}$ 98−101 °C; R_f 0.72 (silica gel, 10% EtOAc/

(26) Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4807.

hexanes); MS *m/z* 151 ($M^+ - 15$); IR (neat) 3285, 2972, 2109, 1732, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.41 (s, 3H), 1.75−1.95 (m, 3H), 2.15 (s, 1H), 2.30 (m, 1H), 2.45 (m, 1H), 4.25−4.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.1, 26.1, 28.2, 33.4, 48.0, 67.7, 69.1, 89.4, 171.3. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.04; H, 8.42.

***N*-Benzyl-2-(3-hydroxypropyl)-3,3-dimethyl-4-pentynamide (42).** This material was prepared in 88% yield following the general procedure outlined above for enamide **38**, employing 166 mg (1.0 mmol, 1.0 equiv) of lactone **41**, and 2.0 mmol (2 equiv) of reagent **31**[18] in 10 mL of anhydrous THF for 24 h at rt. Workup and chromatography (silica gel, 50% EtOAc/hexanes, R_f 0.38) gave 241 mg (88%) of acetylenic amide **42** as a semisolid oil, which on crystallization (hexanes/EtOAc) afforded **42** as colorless grains: mp 96−97 °C; IR (neat) 3299, 3065, 2972, 2109, 1650, 1245, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.42−1.60 (m, 2H), 1.70−1.80 (m, 2H), 1.86 (br, 1H), 2.10 (t, J = 4.4 Hz, 1H), 2.12 (s, 1H), 3.59 (dt, J = 2.5, 2.4 Hz, 2H), 4.41 (d, J = 5.8 Hz, 2H), 6.38 (br, 1H), 7.19−7.32 (m, 5H). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.65; H, 8.52; N, 5.13.

***N*-Benzyl-3-(3-hydroxypropyl)-4,4-dimethyl-5-methylene-2-pyrrolidinone (43).** This material was prepared in 81% yield following the general procedure outlined above for enamide **38**, employing 380 mg (2.29 mmol, 1.0 equiv) of lactone **41** and 2.52 mmol (1.1 equiv) of reagent **31**[18] in 10 mL of anhydrous THF at reflux for 12 h. Workup and chromatography (silica gel, 50% EtOAc/hexanes, R_f 0.50) afforded 506 mg (81%) of enamide **43** as a viscous colorless oil. Alternatively, **43** can be purified by vacuum distillation ($bp_{0.4mm}$ 174−175 °C): IR (neat) 3418, 2962, 2869, 1715, 1662, 1634, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.26 (s, 3H), 1.59−1.88 (m, 4H), 2.31 (m, 1H), 3.68−3.75 (m, 2H), 4.14 (d, J = 2 Hz, 1H), 4.17 (d, J = 2 Hz, 1H), 4.61 (d, J = 15.4 Hz, 1H), 4.72 (d, J = 15.4 Hz, 1H), 7.19−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.7, 27.0, 31.0, 40.5, 43.3, 50.9, 61.8, 83.5, 126.8, 126.9, 128.2, 135.9, 155.5, 176.6. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 73.92; H, 8.44; N, 5.18.

***N*-Benzyl-3-(3-carbomethoxypropyl)-4,4-dimethyl-5-methylene-2-pyrrolidinone (44).** A solution of 950 mg (12.0 mmol, 12.0 equiv) of pyridine in 40 mL of CH_2Cl_2 was cooled to 0 °C and was treated with 600 mg (6.0 mmol, 6.0 equiv) of chromium(VI) oxide (CrO_3) with vigorous stirring. Stirring was continued for an additional 15 min at 0 °C, and the resulting mixture was then treated in dropwise fashion with a solution of 273 mg (1.0 mmol, 1.0 equiv) of alcohol **43** in 5 mL of CH_2Cl_2. After addition was complete, the reaction was allowed to warm to rt and stirring was continued for a period of 30 min. The chromium salts were then separated by decanting, and the supernatant was concentrated under reduced pressure. The residue was triturated with Et_2O, and the residual solid was removed by vacuum filtration through Celite. The filtrate was then washed with 10% NaOH, dried over $MgSO_4$, and concentrated under reduced pressure to afford 241 mg (90%) of aldehyde **43a** as an unstable, light yellow oil that was used without further purification: $bp_{0.25mm}$ 190−192 °C; R_f 0.70 (silica gel, 50% EtOAc/hexanes); MS *m/z* 271 (M^+); IR (neat) 2962, 1715, 1666, 1643, 1260, 1091, 1027, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.26 (s, 3H), 1.79−1.96 (m, 2H), 2.27 (dd, J = 4.6, 9.2 Hz, 1H), 2.82 (m, 1H), 3.02 (m, 1H), 4.13 (d, J = 2 Hz, 1H), 4.17 (d, J = 2 Hz, 1H), 4.59 (d, J = 15 Hz, 1H), 4.69 (d, J = 15 Hz, 1H), 7.18−7.38 (m, 5H), 9.82 (s, 1H); exact mass calcd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1568.

A solution of 543 mg (2.0 mmol, 1.0 equiv) of aldehyde **43a** in 20 mL of anhydrous MeOH was cooled to 0 °C and was treated portionwise, with vigorous stirring, with a solution of 292 mg (5.2 mmol, 2.6 equiv) of potassium hydroxide in 10 mL of MeOH, followed by 660 mg (2.6 mmol, 1.3 equiv) of iodine in 5 mL of MeOH. The resulting solution was stirred for 20 min at 0 °C, and the reaction was then quenched by addition of 10 mL of H_2O. The resulting dark solution was decolorized by addition of 20 mg of $Na_2S_2O_3$. Most of the MeOH was then removed by concentration under reduced pressure, and the aqueous solution remaining was extracted with 3 × 15 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (silica gel, 20% EtOAc/hexanes, R_f 0.68) then afforded 470 mg (78%) of ester **44** as a yellow oil: MS *m/z* 301 (M^+); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.26 (s, 3H), 1.82−1.93 (m, 2H), 2.29 (m, 1H), 2.64 (m, 1H), 2.82 (m, 1H) 3.67 (s, 3H), 4.13 (d, J = 2.3 Hz, 1H), 4.15 (d, J = 2.3 Hz, 1H), 4.59 (d, J = 15.4 Hz, 1H), 4.69 (d, J = 15.4 Hz, 1H), 7.18−7.35 (m, 5H); exact mass calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1672.

Dimethyl 2-(1,1-Dimethyl-2-propynyl)glutarate (46). A solution of 9.30 g (24.0 mmol, 1.0 equiv) of colbalt complex **40**[4h] and 18.50 g (61.0 mmol, 2.5 equiv) of bis-silyl enol ether **45**[23] in 200 mL of CH_2Cl_2 was cooled to −78 °C under nitrogen and was treated in dropwise fashion, with vigorous stirring, with 8.63 g (61.0 mmol, 2.5 equiv) of $BF_3{\cdot}Et_2O$. After addition was complete, the reaction was stirred for an additional 2 h at −78 °C and then for 30 min at 0 °C. The reaction was then carefully quenched with 40 mL of pH 7 buffer and extracted with 3 × 20 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a dark residue. This material could either be purified at this stage (chromatography, silica gel, 10% EtOAc/hexanes) or deprotected directly with no change in yield: R_f 0.4 (silica gel, 5% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.32 (s, 3H), 2.03−2.41 (m, 5H), 3.66 (s, 3H), 3.71 (s, 3H), 6.09 (s, 1H).

A total of 12.23 g (23.0 mmol) of the cobalt-protected Nicholas adduct described above was dissolved in 200 mL of acetone. Ceric ammonium nitrate (CAN) was added in small portions over 30 min, with vigorous stirring, until gas evolution ceased. The solution was then concentrated under reduced pressure, and the resulting red oil was diluted with 100 mL of H_2O. This now orange-colored solution was extracted with 6 × 20 mL of Et_2O, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (silica gel, 10% EtOAc/hexanes) then afforded 4.77 g (94%) of diester **46** as a colorless oil. Alternatively, **46** could be purified by vacuum distillation ($bp_{0.15mm}$ 81−82 °C): R_f 0.45 (silica gel, 40% EtOAc/hexanes); MS *m/z* 226 (M^+); IR (neat) 3285, 2977, 2953, 2109, 1737, 1436, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.27 (s, 3H), 2.04−2.14 (m, 2H), 2.15 (s, 1H), 2.18−2.49 (m, 3H), 3.65 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 26.0, 28.0, 32.3, 51.3, 51.6, 54.3, 69.3, 89.2, 173.1, 173.6. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.47; H, 7.95.

***N*-Benzyl-3-[(*N*-benzylamido)ethyl]-4,4-dimethyl-5-methylene-2-pyrrolidinone (48).** A total of 114 mg (0.5 mmol, 1.0 equiv) of diester **46** was added to a solution of 2.0 mmol (4.0 equiv) of reagent **31**, prepared *in situ* from 76 mg (2.0 mmol, 4.0 equiv) of $LiAlH_4$, 1.1 mL (10.0 mmol, 20.0 equiv) of benzylamine, and 7.0 mL of anhydrous THF following the general procedure of Solladié-Cavallo.[18] After addition was complete, the reaction mixture was heated at reflux for a period of 8 h. After being cooled to rt, the reaction mixture was then carefully quenched by sequential addition of 1.0 mL of H_2O, 1.0 mL of 10% NaOH, and 3.0 mL of H_2O. Stirring was continued until the new precipitate became white and powdered. The mixture was then filtered through Celite and washed thoroughly with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed (silica gel, 50% EtOAc/hexanes, R_f 0.60) to afford 152 mg (81%) of enamide **48** as a semisolid colorless oil: MS *m/z* 376 (M^+); IR (neat) 3311, 3063, 2964, 1712, 1659, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.21 (s, 3H), 1.72 (m, 1H), 2.05 (m, 1H), 2.23 (m, 1H), 2.51−2.70 (m, 2H), 4.13 (d, J = 2 Hz, 1H), 4.17 (d, J = 2 Hz, 1H), 4.43−4.47 (m, 2H), 4.58 (d, J = 15.4 Hz, 1H), 4.67 (d, J = 15.4 Hz, 1H), 6.48 (br, 1H), 7.15−7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 23.4, 27.7, 34.1, 40.6, 43.4, 43.5, 49.9, 84.1, 127.0, 127.3, 127.7, 128.5, 136.1, 138.5, 155.5, 172.5, 176.6; exact mass calcd for $C_{24}H_{28}N_2O_2$ 376.2151, found 376.2146.

3-[(*N*-Benzylamido)ethyl]-4,4-dimethyl-5-methylene-2-pyrrolidinone (49). Approximately 10 mL of liquid NH_3 was distilled from Na metal through a glass tube into a three-

necked flask containing 197 mg (0.52 mmol, 1.0 equiv) of *N*-benzylenamide **48** and equipped with a dry ice/acetone condenser. The reaction mixture was then treated with 48 mg (2.09 mmol, 4.0 equiv) of Na metal to give a dark blue solution. This solution was maintained at −33 °C for 10 min (reflux) and was then carefully quenched by slow addition of ammonium chloride to produce a thick white suspension. The suspension was vigorously mixed to ensure complete quenching of the Na (**Warning**: as with all Na reductions, possible fire hazard). The NH_3 was then allowed to evaporate at rt, and the residue was partitioned between 10 mL of CH_2Cl_2 and 10 mL of H_2O. The layers were separated, and the aqueous layer was extracted with an additional 2 × 10 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (silica gel, CH_2Cl_2) then afforded 99 mg (98%) of the debenzylated enamide **49** as an unstable colorless oil: R_f 0.6 (silica gel, 50% EtOAc/hexanes); MS *m*/*z* 286 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.23 (s, 3H), 1.69 (m, 1H), 1.98 (m, 1H), 2.14 (m, 1H), 2.42−2.65 (m, 2H), 4.10 (d, J = 2 Hz, 1H), 4.23 (d, J = 2 Hz, 1H), 4.40−4.46 (m, 2H), 6.51 (br, 1H), 7.20−7.35 (m, 5 H), 7.49 (br, 1H).

Acknowledgment. Financial support of this work by the National Institutes of Health, Grant No. GM38913, is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **18b**−**d**, **19b**−**d**, (*Z*)-**21a**−**f**, (*E*)-**21a**,**b**, **23a**−**f**, **24b**−**d**, **25b**−**d**, **26c**, **27a**−**f**, **28b**−**d**, **29b**−**d**, **30c**, **36**, **38**, **41**−**44**, **43a**, **46**, **48**, and **49** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960428+