Studies on the Synthesis of Phytochrome and Related Tetrapyrroles. Dihydropyrromethenones by Photochemical Rearrangement of *N*-Pyrrolo Enamides

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Dihydropyrromethenone **67b**, a potential precursor for the synthesis of phytochrome **1**, has been prepared in enantiomerically pure form beginning with *N*-aminopyrrole **64** and the acetylenic acid **62b**. The key step involved a 3,5-sigmatropic rearrangement of *N*-pyrrolo enamide **66b**.

Introduction

The biliproteins are a family of naturally occurring chromophores that are made up of linear tetrapyrrole derivatives covalently bonded to a protein (P).[1−7] Representative examples include phytochrome **1**, which functions as the "on-off" switch for photomorphogenesis in higher plants,[6,7] the phycocyanins **2**, and phycoerythrins **3** (Figure 1).[8,9] Tetrapyrroles **2** and **3** are commonly

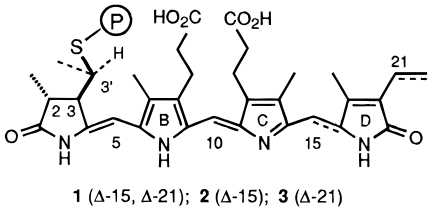

Figure 1.

found in blue-green, eucaryotic and cryptomonad algae and serve as light-harvesting proteins in photosynthesis. Phytochrome (**1**) plays an essential role in many light-dependent, irreversible processes, including seed germination, flowering, and stem growth. It has also been implicated in such reversible phenomena as chloroplast movement, root tip adhesion, potassium uptake, and regulation of transmembrane potentials.[2,6]

It is now well established that **1** can exist in either of two possible forms in plants: an inactive red-absorbing form known as **Pr** (λ_{max} 660 nm) and an active, far red absorbing form designated as **Pfr** (λ_{max} 730 nm).[10−14] These two species are readily interconverted upon irradiation at 660 and 730 nm, respectively, a photoreversible−photochromic behavior which has been the subject of intensive study for many years.[2−7] However, at present only the structure of the **Pr** form of **1** is known with some degree of certainty (Figure 2).[11a,12] In the

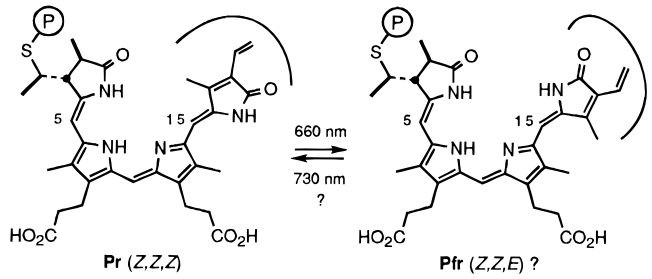

Figure 2.

native state **Pr** most likely adopts a helical geometry (all *Z* configuration), incorporating a 15-*anti* conformation.[12c,d] Among other theories, it has been suggested that **Pfr** might be derived from **Pr** by (a) formation of an imino ester linkage at C_1, thereby extending the effective chromophore conjugation,[11a,b] (b) photoreversible *Z*,*E* isomerization about the C_4-C_5 double bond,[12a] and, as illustrated, (c) photoisomerization about the $C_{15}-C_{16}$ bond, with retention of a "semi-extended" chromophore conformation.[12b−d]

According to this last model, photoisomerization induces a change in the tertiary structure of the surrounding protein shell (curves in Figure 2), thereby providing

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(3) Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*; Springer-Verlag: Vienna−New York, **1989**.
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(14) (a) Scheer, H.; Krauss, C. *Photochem. Photobiol.* **1977**, *25*, 311. (b) Scheer, H.; Linsenmeier, U.; Krauss, C. *Hoppe-Seyler's Z. Physiol. Chem.* **1977**, *358*, 185. (c) Krauss, C.; Bubenzer, C.; Scheer, H. *Photochem. Photobiol.* **1979**, *29*, 473.

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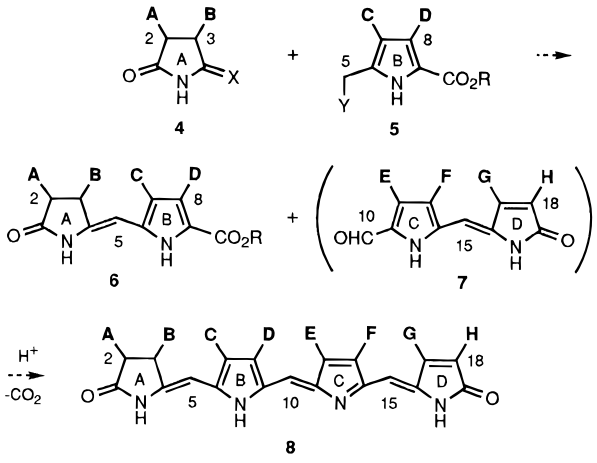
a molecular basis for transduction of the light signal to the cells genetic regulatory apparatus. This proposal gains support from both NMR[12b] and SE resonance raman scattering spectroscopy (SERRS),[12c,d] although at present the data are not conclusive. In part this is due to the extremely small quantities of phytochrome **1** available for study from natural sources. Even in seedlings grown in the dark (etiolated), and therefore free of chlorophyll, the deep blue color of photoreceptor **1** is difficult to detect. In this paper, and the accompanying article, we describe synthetic studies which provide a basis for the preparation of naturally occurring chromophores of type **1**−**3** with unequivocal control over both relative and absolute stereochemistry. Ultimately these studies might lead to a better understanding of the phenomenon of photomorphogenesis.

Discussion and Results

Most of the published work in this area has been carried out on simple model compounds and has utilized either of two synthetic strategies. The first of these is based on biosynthetic theory and involves the oxidative cleavage of porphyrins, chlorins, and related materials.[15] Although this approach can be of occasional utility when applied to unsymmetrical derivatives, it cannot provide the variety of biliproteins required for detailed study. As a more general strategy, suitably functionalized pyrromethenone derivatives of type **6** and **7** can frequently be coupled to yield linear tetrapyrrole derivatives **8** in moderate to good yields (Scheme 1).[16] In principle, this

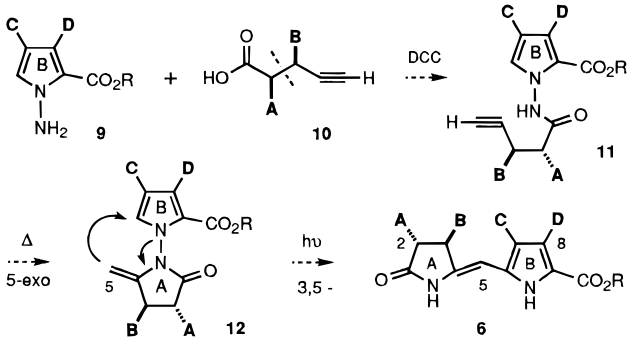
Scheme 1



approach provides satisfactory control over both stereo- and regiochemical features (A−H in **8**) as well as oxidation state at crucial ring positions. However, this second strategy is limited by the availability of the pyrromethenone derivatives themselves, which are typically derived by coupling of monocyclic building blocks of type **4** and **5**. These last two species present significant synthetic challenges in their own right, which are compounded by the fact that coupling of **4** and **5** to afford **6** is often not a trivial problem.[16a,b]

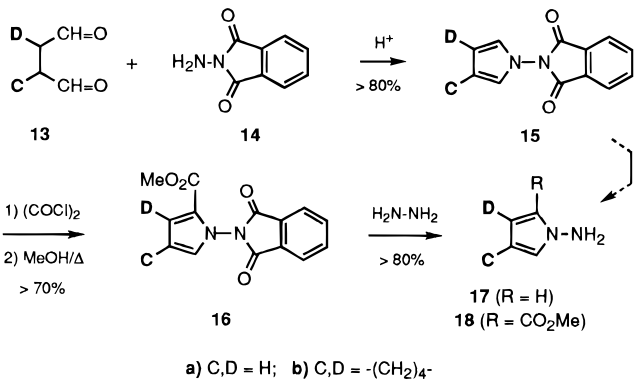
As an alternative strategy, we were interested in the possibility that dihydropyrromethenones of general structure **6** might be prepared beginning with *N*-aminopyrroles of type **9** (Scheme 2). By way of summary, *N*-acylation of **9** with acetylenic acid derivatives of type **10** was expected to yield the *N*-pyrroloamides **11**, which upon 5-*exo*-*dig* cyclization would give *N*-pyrrolo enamides of general structure **12**. Enamides **12**, upon 3,5-sigmatropic rearrangement[17] and subsequent aromatization, would then afford dihydropyrromethenones **6** with complete control over both relative and absolute stereochemistry. An attractive feature of this strategy was the fact that stereochemical and regiochemical features incorporated into **10** would be transposed in an unequivocal fashion to the final product **6**. As will be reported, there was reason to believe that acyclic intermediates **10** could be synthesized in enantiomerically pure form using a Nicholas reaction (dashed line in **10**, *vide infra*).[18]

Scheme 2



The feasibility of this strategy was initially tested with the simple model systems **17** and **18**, which, because of their symmetrical nature (**C**, **D** = H, cyclohexyl), were readily prepared by following standard literature proce-

Scheme 3



a) C,D = H; **b)** C,D = -$(CH_2)_4$-

(15) See, for example: (a) Smith, K. M.; Kishore, D. *Tetrahedron* **1983**, *39*, 1841. (b) Cavaleiro, J. A. S.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2149. (c) Barnett, G. H.; Hudson, M. F.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 691. (d) Smith, K. M.; Sharkus, L. C.; Dallas, J. L. *Biochem. Biophys. Res. Commun.* **1980**, *97*, 1370. (e) Bonnett, R.; McDonagh, A. F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 881.

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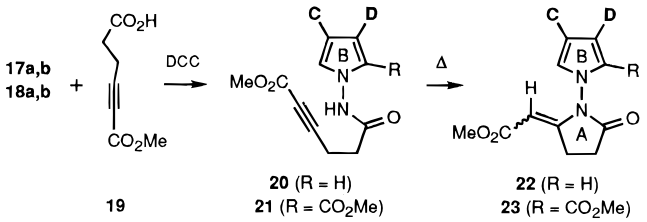
(18) (a) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. (b) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. See also: (c) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163. (d) Nicholas, K. M.; Nestle, M. O.; Deyferth, D. *Transition Metal Organometallics*; Alper, H., Ed.; Academic Press: New York, **1978**; Vol. 2, p 1. (e) Evans, D. A.; Ennir, M. D., Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

dures (Scheme 3).[19] Thus, condensation of *N*-aminophthalimide (**14**) with dialdehydes **13a,b** gave an excellent yield of the protected *N*-aminopyrroles **15a,b**, which could be directly cleaved to the aminopyrroles **17a,b** with hydrazine in ethanol or converted to the methyl esters **16a,b** with oxaloyl chloride/$AlCl_3$ followed by methanolysis.[20] Hydrazinolysis of **16a,b** then proceeded routinely to afford the amino esters **18a,b** with no complications due to ester aminolysis. Once in hand, both **17a,b** and **18a,b** were cleanly coupled with the acetylenic acid **19** to provide the hydrazide derivatives **20a,b** and **21a,b** (Scheme 4). As expected for electron deficient alkynes,

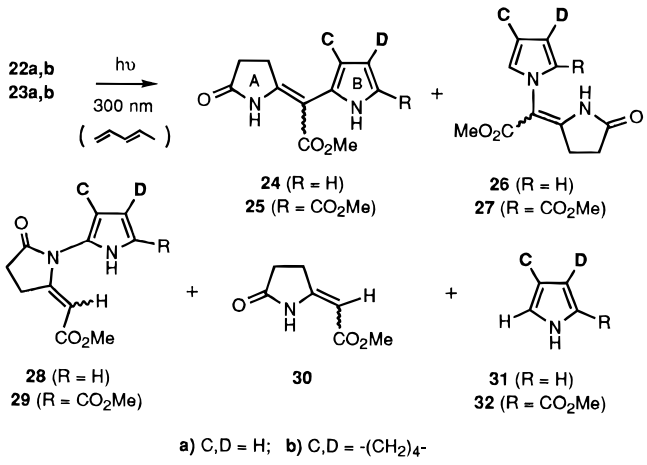
Scheme 4



these last materials then underwent a facile 5-*exo*-*dig* cyclization to afford either **22a,b** or **23a,b** in >90% yield (~3:1 mixture of *E*- and *Z*-isomers). This step completed the formation of rings A and B.

Numerous conditions were examined for converting **22a,b** and **23a,b** to the isomeric pyrromethenones **24a,b** and **25a,b** (Scheme 5). These materials were stable to

Scheme 5



thermolysis at temperatures up to 250 °C,[17c] and at higher temperatures they suffered only slow decomposition to intractable tars. Also, all attempts at acid catalysis led to decomposition. Upon photolysis, however, **22a,b** and **23a,b** gave reaction mixtures which contained trace amounts of the desired products of 3,5-sigmatropic shift (**24**, **25**), in addition to products corresponding to 1,3- and 1,5-sigmatropic shifts (**26**−**29**) and N-N bond cleavage (**30**−**32**). After considerable experimentation, we found that the ratio of products **24**-**32** was strongly influenced by the presence or absence of triplet state quenchers. For example, at 300 nm **22a** (*E*- or *Z*-isomer) gave 5−10% yields of the rearrangement products **24a**, **26a**, and **28a**, together with a larger proportion of the cleavage products **30** and **31a**. Similar results were obtained at 253 nm. Significantly, cleavage products **30**−**32** were the only products observed in the presence of triplet sensitizers. In the presence of piperylene (triplet quencher),[21] however, cleavage was reduced to trace amounts, and **24a** was obtained in 40−50% yield as an equilibrium mixture of *E* and *Z* isomers (~1:1). Similar results were obtained with **22b**, and in identical fashion, **23a,b** afforded 40−50% yields of the target pyrromethenones **25a,b**.[22] These studies are consistent with a reaction pathway in which photodissociation occurs *via* a triplet state, in competition with a singlet state 3,5-sigmatropic shift. Although the yields obtained in the conversion of **22** and **23** to the dihydropyrromethenones **24** and **25** were not as high as might be desired, we were sufficiently encouraged to pursue additional studies with substrates bearing the natural substitution pattern.

In order for these preliminary studies to be extrapolated to the preparation of dihydropyrromethenones of general structure **35** (a logical precursor to **1**−**3**), it was first necessary to devise efficient syntheses of both *N*-aminopyrroles of type **33** and highly substituted acetylenic acids of type **34** (Figure 3). As in the case with

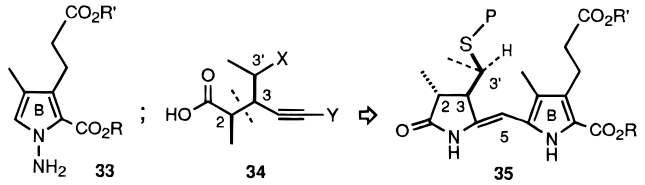
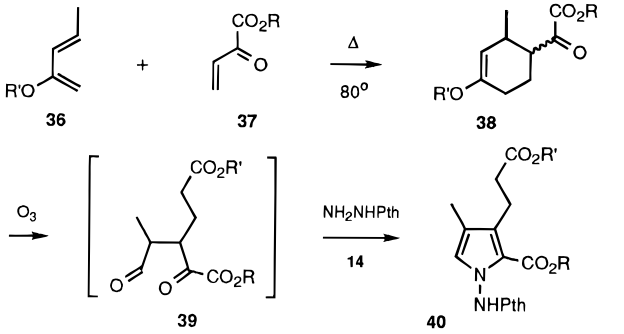


Figure 3.

N-*un*substituted pyrroles, the synthesis of **33** required strict control of regiochemistry, which turned out to present a significant challenge. Ultimately, however, these materials were derived by following the route outlined in Scheme 6, which takes advantage of a highly *ortho*-selective Diels−Alder reaction of 2-alkoxy-1,3-pentadiene derivatives **36** with 2-oxo-3-butenoate esters **37**.[23]

Scheme 6



Adducts **38** were then converted to protected *N*-aminopyrroles **40** by a two-step sequence involving ozonolysis to afford 1,4-dicarbonyl species **39**, followed by Paal−Knorr cyclization with *N*-aminophthalimide (**14**). Finally, as described in Scheme 3, hydrazinolysis of **40** gave a virtually quantitative yield of the target pyrroles **33**.

(19) Zimmerman, H.; Flitsch, W.; Kramer, V. *Chem. Ber.* **1969**, *102*, 3268.

(20) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.

(21) (a) Hammond, G. S.; Turro, N. J.; Leermakers, P. A. *J. Phys. Chem.* **1962**, *66*, 1144. (b) Yang, N. C.; Hui, M. H.; Shold, D. M.; Turro, N. J.; Hautala, R. R.; Dawes, K.; Dalton, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 3023.

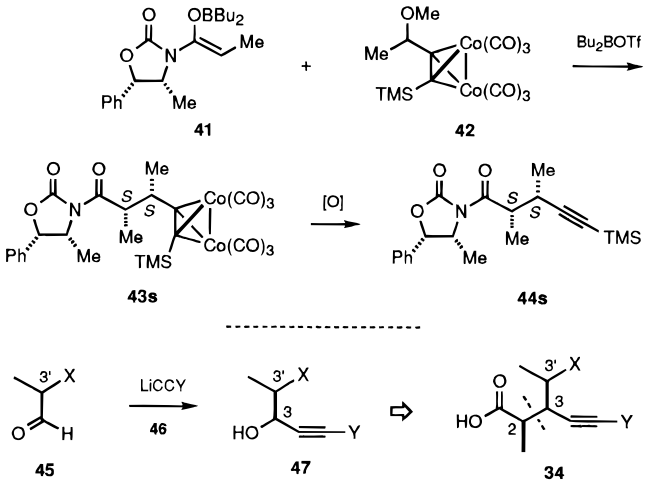
(22) The structure of dihydropyrromethenone **25b** (*E* isomer) and acetylenic acid **62c** were unequivocally established by single-crystal X-ray analysis: performed by Ms. Gayle Schulte, Yale University.

(23) Jacobi, P. A.; Cai, G. *Heterocycles* **1993**, *35*, 1103.

Since the ozonolysis products **39** were generally not isolated, this route constitutes a convenient three-step sequence for preparing **33** from readily available starting materials.

Our synthesis of acetylenic acids **34** built upon work by Schreiber *et al.*, who first demonstrated that Nicholas alkylations can be carried out with high enantioselectivity.[18] In an elegant mechanistic study, this group observed that Bu_2BOTf-catalyzed condensation of Evans' enolate **41** with the cobalt complex **42** occurs with kinetic resolution,[18e] affording an ~80% yield of the *syn*-adduct **43s** having exclusively the *S,S* configuration (Scheme 7; *syn:anti* selectivity = 12:1).[18a] Oxidative removal of cobalt

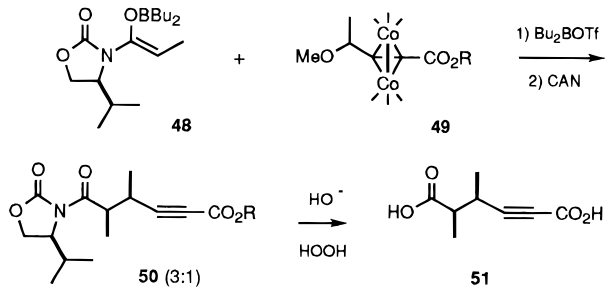
Scheme 7



then gave a quantitative yield of the alkyne **44s**. This work provided excellent precedent for the synthesis of acetylenic acids of type **34** (Scheme 7). By analogy, we were confident that reaction of aldehydes of general structure **45** with acetylides **46** would afford propargyl alcohol derivatives **47**, which upon Nicholas–Schreiber condensation with an appropriate chiral enolate would give ring-A precursors **34** with unequivocal control over stereochemistry at C_2, C_3, and $C_{3'}$ (tetrapyrrole numbering). The flexibility of this approach might be put to good advantage in confirming the postulated relative and absolute stereochemistry in **1**–**3**.

We initially expected that alkynes of type **34** would be of greatest utility when Y = carbalkoxy, since it appeared that an electron deficient triple bond was required for 5-*exo*-*dig* cyclization (*cf.* Scheme 4). Therefore, our preliminary studies focused on preparing simple dimethyl analogs of type **50a**–**c**, which were synthesized in analogous fashion to **44s** but employing the chiral oxazolidinone **48** (Scheme 8). In this case, however, we were disappointed to find that *syn*-selectivity in the reaction **48** + **49** → **50** was only ~3:1 (60–80% yield).

Scheme 8

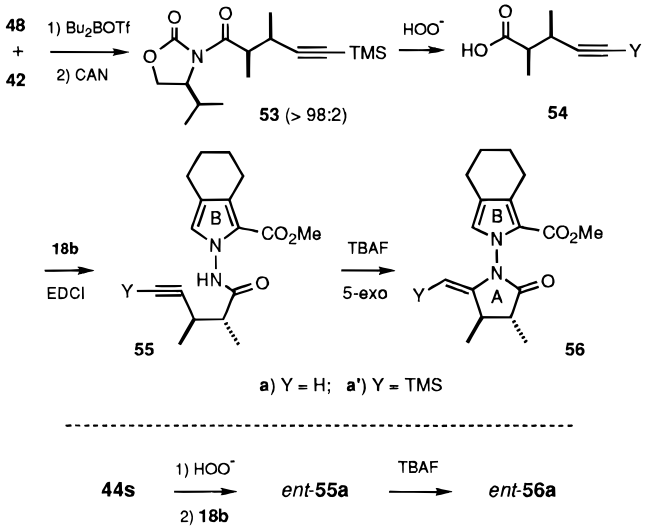


a) R = Me; **b**) R = *t*-Bu; **c**) R = Bn

This result is in general accord with the observations of Schreiber *et al.*, who noted that selectivity increases with increasing size of Y.[18a,b] Equally disappointing, we were unable to selectively remove the chiral auxiliary in **50** without concomitant hydrolysis of the acetylenic ester to afford diacid **51**.[24] This lack of differentiation was a serious complication, since all attempts at monofunctionalization of **51** invariably led to complex mixtures of products.

In contrast to the poor selectivity observed with esters **49a**–**c** (Scheme 8), trimethylsilyl derivative **42** underwent clean condensation with oxazolidinone **48**, affording Nicholas adduct **53** in 90–95% yield with >98% *syn* selectivity (Scheme 9; this selectivity is significantly higher than that observed with oxazolidinone **41**[18b]). This

Scheme 9



reaction clearly demonstrated the potential for achieving stereoselectivities of the level desired for the synthesis of **1**–**3**. Adduct **53** was then readily converted to the acetylenic hydrazide **55a** (Y = H) by a two-step sequence involving hydrolysis to the acetylenic acid **54a** (concomitant removal of TMS group)[24] and EDCI-catalyzed coupling with *N*-aminopyrrole **18b**.

At this stage, we experienced considerable difficulty in effecting the required 5-*exo*-*dig* cyclization leading from **55a** to enamide **56a** (Scheme 9). Not surprisingly, **55a** was inert to cyclization under thermal conditions, and it rapidly decomposed upon attempted acid or base catalysis. These results are in marked contrast to the ease of cyclization of activated alkynes of type **20** and **21** (*cf.* Scheme 4). In addition, solvomercuration–demecuration took place mainly with participation of the hydrazide carbonyl group to give modest yields of cyclic imino esters. Eventually, some degree of success was achieved with the reagent system $PdCl_2(MeCN)_2$/NaOAc, which afforded 60–70% yields of the desired enamide **56a**.[25,26] This reaction was also accompanied by significant amounts of alkyne coupling. However, by far the most useful procedure was discovered in a serendipitous fashion upon attempted cleavage of the trimethylsilyl group from acetylenic hydrazide **55a′** (Y = TMS). This

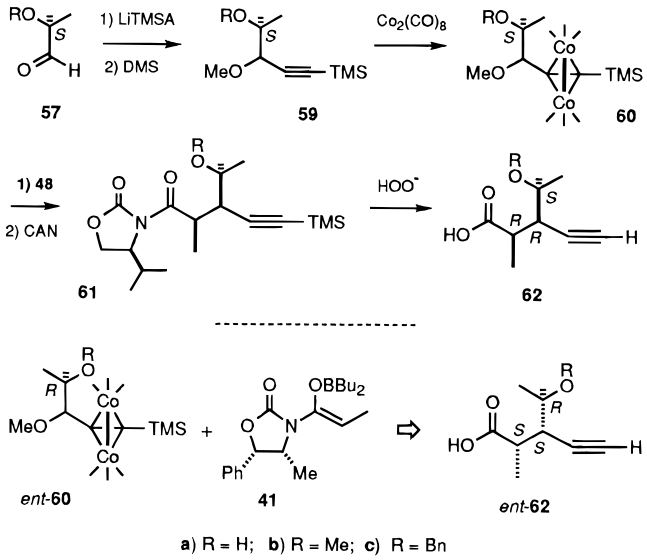
(24) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(25) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.
(26) As expected, enamides **56** exhibited atropisomerism due to hindered N–N bond rotation, although each isomer had identical photochemical behavior. See, for example, ref 3, p 108.

material was obtained from adduct **53** by hydrolysis and amidation under carefully controlled conditions. **55a′** afforded none of the expected terminal alkyne **55a** upon being warmed with *n*-Bu_4NF (TBAF), but rather was directly converted to the identical *N*-pyrrolo enamide **56a** obtained from Pd(II)-catalyzed cyclization of **55a**. The same conditions, when applied to terminal alkyne **55a**, afforded enamide **56a** in 70−90% yield. The precise mechanism by which the fluoride ion catalyzes the cyclization of **55a,a′** to **56a** is not known with certainty, but it presumably involves a strong hydrogen bond between F− and the hydrazide N−H group, with an attendant increase in *N*-nucleophilicity.[27] In any event, we utilized an identical two-step sequence to convert adduct **44s** to the enantiomeric hydrazide *ent*-**55a** (*ent* = mirror image of structure shown), which when warmed with TBAF gave an excellent yield of enamide *ent*-**56a**. As with **56a** above, *ent*-**56a** was obtained as a single enantiomer.

With the problem of hydrazide cyclization apparently solved, we turned our attention next to preparing acetylenic acids having the proper constitution for eventual conversion to **1**−**3**. In phytochrome (**1**) the absolute stereochemistry at C_2 and C_3 has been assigned as *R*, but it is important to maintain as much flexibility as possible in the synthetic scheme. As summarized in Scheme 7 (**45** → **34**), we intended that both relative and absolute stereochemistry at C_2−C_3 would be controlled through the use of an enantioselective Nicholas reaction (*vide supra*), while stereochemistry at $C_{3'}$ (also believed to be *R*) would be established by utilizing an appropriate aldehyde **45** from the "chiral pool". In principle, the aldehyde chosen could incorporate a sulfur ligand of proper absolute configuration from the start (X = S−R). Alternatively, the desired configuration could be obtained by nucleophilic displacement with inversion of an activated hydroxyl group at a later stage of the synthesis (X = O−R).[28] This second approach offered a greater degree of flexibility, and it also had the advantage that both *R*- and *S*-α-hydroxyaldehyde derivatives of the required composition are readily available from (*R*)- and (*S*)-lactic acid, respectively.[29]

Our expectations regarding the utility of the Nicholas reaction turned out to be fully justified (Scheme 10).

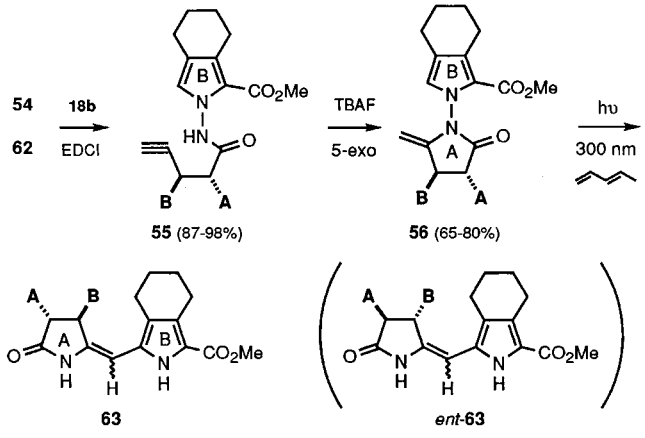
Scheme 10



Thus, condensation of lithium (trimethylsilyl)acetylide (LiTMSA) with aldehydes **57b** and **57c** afforded 90−95% yields of the corresponding acetylenic alcohols **58b,c**,[29] which without isolation were methylated (DMS) to give the methyl propargyl ethers **59b,c** in excellent overall yield. Conversion of **59b,c** to the cobalt complexes **60b,c** was then accomplished by following standard literature procedures.[18] Reaction of **60b,c** with the chiral boron enolate **48** then gave the Nicholas adducts **61b,c** (>95%), which upon hydrolysis provided the target (2*R*,3*R*,3'*S*)-acetylenic acid derivatives **62b,c** in 60−70% overall yield from aldehydes **57**.[22] In both cases *syn*-stereoselectivity was >98%. In identical fashion, (2*S*,3*S*,3′*R*)-acetylenic acids *ent*-**62** were prepared with similar yields and selectivities by utilizing the boron enolate **41**.

As described above for the acetylenic acids **54** and *ent*-**54** (Scheme 9), acetylenic acids **62b**,**c** were readily converted to the corresponding *N*-pyrrolo enamides **56b**,**c** by a two-step sequence involving EDCI-mediated coupling with *N*-aminopyrrole **18b**, followed by TBAF-catalyzed cyclization (Scheme 11). Enantiomerically pure

Scheme 11



Cmpd	A	B	Yield	$[\alpha]^{25}_D$ (*Z*)
63a	Me	Me	39% (42%)*	+40.18°
63b	Me	*S*-$CHOMeCH_3$	37% (47%)*	-20.82°
63c	Me	*S*-$CHOBnCH_3$	trace	-
63d	H	H	60% (78%)*	0.00°
ent-**63a**	Me	Me	46% (51%)*	-40.98°

* Yield based on recovered starting material

enamides **56a**−**c** and *ent*-**56a**, as well as achiral enamide **56d**, were then subjected to photochemical rearrangement, using conditions similar to those employed for model systems **22** and **23** (300 nm, *tert*-amyl alcohol, piperylene, −10 °C; *cf.* Scheme 5). In general, yields for this step were moderate to good, ranging from a low of 37% for **63b** to 78% for **63d** (see table). Dihydropyrromethenones **63** were obtained as ∼1:1 mixtures of *E* and *Z* isomers. In analogous fashion, enamide *ent*-**56a** gave the enantiomeric dihydropyrromethenone *ent*-**63a**, which within experimental error had equal but opposite $[\alpha]^{25}_D$ to that observed for **63a** (*Z* isomers).

(27) (a) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644. (b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429. (c) Morrison, H. *J. Am. Chem. Soc.* **1965**, *87*, 932. (d) Jacobi, P. A.; Rajeswari, S. *Tetrahedron Lett.* **1992**, *33*, 6235.

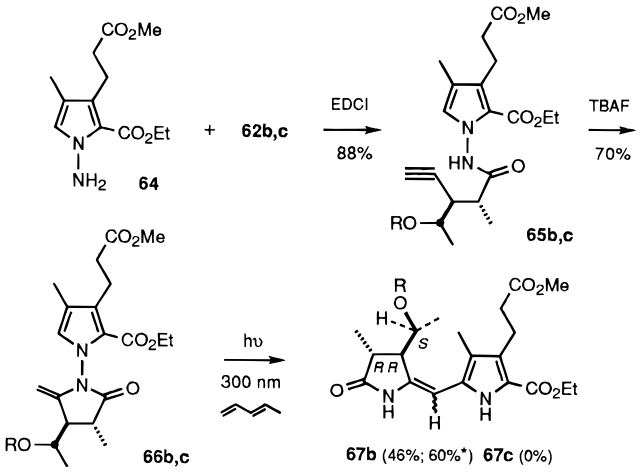
(28) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119 and references cited therein.

(29) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247 and references cited therein.

As in the case with enamides **22** and **23** (Scheme 5),[17a] satisfactory yields of **63** and *ent*-**63** were obtained only in the presence of piperylene (triplet quencher), which minimizes the formation of byproducts arising from hydrazide cleavage. Interestingly, benzyl ether **56c** (**A** = Me, **B** = *S*-CHO*Bn*CH_3) and methyl ether **56b** (**A** = Me, **B** = *S*-CHO*Me*CH_3) showed markedly different behavior upon attempted photochemical rearrangement. Thus, **56b** afforded a ~40% yield of dihydropyrromethenone **63b** after 21 h at −10 °C (300 nm), while **56c** reacted only very slowly to give mainly the products of hydrazide cleavage (<5% of desired **63c** after 48 h). This result was not entirely unexpected, since **56c** contains a phenyl group which might be capable of internal triplet sensitization (*vide supra*).[30] However, it serves to emphasize the fact that care must be taken in choosing protecting groups for the $C_{3'}$ position (R in **62**).

Finally, we were pleased to find that *N*-pyrroloamide **65b** (R = Me), prepared in 88% yield from *N*-aminopyrrole **64** and acetylenic acid **62b**,[23] could be converted in analogous fashion to enamide derivative **66b** (70%), and subsequently to dihydropyrromethenone **67b** by photochemical rearrangement (Scheme 12; 46% yield; 60% based on recovered **66b**). Compound **67b**, which was

Scheme 12



a) R = H; **b**) R = Me; **c**) R = Bn

obtained as a single enantiomer, has all of the structural features necessary for eventual conversion to **1**−**3**. As in the case with **63c** (Scheme 11), benzyl-protected enamide **66c** suffered only hydrazide cleavage upon photolysis under identical conditions, presumably due to triplet sensitization.

Summary

A photochemical strategy for the synthesis of enantiomerically pure ring-A,B synthons of linear tetrapyrroles **1**−**3** has been tested with encouraging results for a number of dihydropyrromethenones of type **6** (Scheme 2). The utility of this approach stems partly from the fact that a wide variety of acetylenic acids **10** (and *ent*-**10**) are available by Nicholas−Schreiber reaction of chiral ester enolates with cobalt-stabilized propargylic cations.[18] In addition, ring-B precursors of type **9** can be prepared with unequivocal control over regiochemistry.[23] These developments provide for a considerable degree of flexibility in the introduction of substituents A−D in tetrapyrroles of general structure **8**. Further discussion of the utility of acetylenic acids **10** for the construction of linear tetrapyrroles can be found in the accompanying paper.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 400 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.

Hexahydrophthalaldehyde (13b). A solution of 6.87 g (54.0 mmol) of oxalyl chloride in 370 mL of CH_2Cl_2 was cooled to −78 °C and was treated in dropwise fashion, with vigorous stirring, with 9.1 g (108.0 mmol) of DMSO over a period of 1 h. The resulting solution was then treated with a total of 2.98 g (20.7 mmol) of *cis*-1,2-cyclohexanedimethanol over a period of 3 h. After the mixture was stirred for an additional 20 min, it was treated with 21.0 g (208.0 mmol) of NEt_3 over a period of 30 min and the resulting mixture was allowed to warm slowly to rt. After the mixture was stirred for an additional 15 h at rt, 93 mL of H_2O was added and the reaction mixture was extracted with 3 × 100 mL of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to afford 2.03 g (70%) of **13b** as an unstable yellow oil, which was used immediately in the next step: IR ($CHCl_3$) 2932, 1722, 1448, 1208 cm^{-1}.

2-Phthalimido-4,5,6,7-tetrahydro-2*H*-isoindole (15b). A solution of 0.55 g (3.93 mmol) of **13b** and 0.71 g (3.93 mmol) of *N*-aminophthalimide in 46 mL of THF was warmed to 40 °C and was treated in a dropwise fashion, with vigorous stirring, with 0.3 mL of 5.0 N HCl. After the adddition was complete, the reaction mixture was stirred for an additional 20 min at rt before diluted with 20 mL of H_2O and extracted with 3 × 50 mL of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to afford 0.85 g (81%) of **15b** as a pale yellow microcrystalline solid: mp 244−6 °C; IR ($CHCl_3$) 3019, 2932, 1745, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.58 (s, 4H), 6.38 (s, 2H), 7.82 (m, 2H), 7.94 (m, 2H). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.08; H, 5.33; N, 10.47.

1-Carbomethoxy-2-phthalimido-4,5,6,7-tetrahydro-2*H*-isoindole (16b). A solution of 25.0 g (0.20 mol) of $AlCl_3$ in 80 mL of 1,2-dichloroethane was cooled to 0 °C and was treated with a total of 18.0 mL (0.20 mol) of oxalyl chloride over a period of 1.5 h. The resulting solution was then treated in a dropwise fashion, with vigorous stirring, with 2.0 g (7.5 mmol) of **15b** in 80 mL of CH_2Cl_2, maintaining a temperature of 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at rt for 8 days. The resulting black solution was poured into 1600 mL of ice water and extracted with 3 × 200 mL of Et_2O. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a black residue, which was dissolved in 200 mL of absolute MeOH. This solution was heated at reflux for 1 h before being concentrated under reduced pressure to afford a dark residue. Chromatography (silica gel, 30% EtOAc/hexanes) then gave 2.0 g (82%) of **16b** as a yellow crystalline solid: mp 157−8 °C (from EtOAc/hexanes); R_f 0.60 (silica gel, 30% EtOAc/hexanes); MS *m*/*z* 324 (M^+); IR ($CHCl_3$) 3032, 2938, 1748, 1695, 1441, 1401, 1298, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.57 (t, 2H, J = 6.0 Hz), 2.81 (t , 2H, J = 6.0 Hz), 3.63 (s, 3H) 6.63 (s, 1H), 7.80 (m, 2H), 7.97 (m, 2H). Anal. Calcd for $C_{18}H_{16}O_4N_2$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.75; H, 5.02; N, 8.60.

1-Phthalimido-2-carbomethoxy-1*H*-pyrrole (16a). In a fashion identical to that described above for **16b**, 8.9 mmol of **15a** afforded 2.2 g (90%) of pyrrole **16a** as a yellow solid: mp 161−2 °C; R_f 0.30 (silica gel, 30% EtOAc/hexanes); MS *m*/*z* 270 (M^+); IR (KBr) 3090, 3015, 2980, 1750, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 6.35 (m, 1H), 6.97 (m, 1H), 7.08 (m,

(30) Morrison, H. *J. Am. Chem. Soc.* **1965**, *87*, 932.

1H), 7.82 (m, 2H), 7.96 (m, 2H). Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.25; H, 3.74; 10.28.

General Procedure for Phthalimide Hydrazinolysis. A solution of ~5 mmol of the appropriate phthalimidopyrrole **15** or **16** in 20 mL of absolute EtOH was treated with vigorous stirring with 1.1 equiv of hydrazine monohydrate at rt. The reaction mixture was homogeneous at the beginning, but a white precipitate separated with time. After the mixture was stirred for a total of 2 h, the precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O, and the aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed to afford the desired aminopyrrole.

1-Aminopyrrole (17a). This material was prepared in 70% yield as a pale yellow oil beginning with 5.2 mmol of **15a**: R_f 0.44 (silica gel, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 4.83 (br s, 2H), 6.04 (t, 2H, J = 2.75 Hz), 6.69 (t, 2H, J = 2.75Hz).

2-Amino-4,5,6,7-tetrahydro-2*H*-isoindole (17b). This material was prepared in 85% yield as a yellow oil beginning with 3.6 mmol of **15b**: R_f 0.30 (silica gel, 30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 4H), 2.51 (m, 4H), 4.73 (br s, 2H), 6.37 (s, 2H).

1-Amino-2-carbomethoxy-1*H*-pyrrole (18a). This material was prepared in 82% yield as colorless needles, mp 43−4 °C, beginning with 2.6 mmol of **16a**: R_f 0.90 (90% Et_2O/hexanes); MS m/z 140 (M^+); IR ($CHCl_3$) 3346, 3012, 2945, 1692, 1438, 1218, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 6.01 (m, 1H), 6.82 (m, 1H), 6.95 (m, 1H), 5.16 (br s, 2H). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.68; H, 5.82; N, 19.79.

1-Carbomethoxy-2-amino-4,5,6,7-tetrahydro-2*H*-isoindole (18b). This material was prepared in 76% yield as colorless crystals, mp 77−8 °C, beginning with 0.38 mmol of **16b**: R_f 0.40 (30% EtOAc/hexanes); MS m/z 194 (M^+); IR (KBr) 3326, 2932, 2845, 1688, 1444, 1404, 1257, 1990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 4H), 2.45 (t, 2H, J = 6.0 Hz), 2.71 (t, 2H, J = 6.0 Hz), 3.80 (s, 3H), 5.45 (br s, 2H), 6.67 (s, 1H). Anal. Calcd for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.76; H, 7.32; N, 14.41.

5-Carbomethoxy-4-pentynoic Acid (19). A solution of lithium diisopropylamide (LDA) in THF was prepared from 5.6 mL of diisopropylamine in 60 mL of anhydrous THF, cooled with stirring to −78 °C, and 16.0 mL of 2.5 M *n*-butyllithium/hexanes. The resulting solution of LDA was stirred for an additional 1 h at −78 °C and was then warmed to −60 °C before being treated in a dropwise fashion, with vigorous stirring, with a solution of 1.96 g (20.0 mmol) of 4-pentynoic acid in 28 mL of HMPA. The temperature in the reaction mixture was maintained at −50 °C throughout. After the addition was complete (~40 min), stirring was continued at −50 °C for an additional 1 h before the reaction mixture was treated in a dropwise fashion with a solution of 1.54 mL (20.0 mmol) of methyl chloroformate in 27 mL of THF (the rate of addition was controlled so as to maintain the dianion in solution as the reaction temperature was kept below −50 °C). After the dark mixture was stirred for an additional 30 min at −50 °C, the reaction was quenched with 2.3 mL (1 equiv) of glacial HOAc and the mixture allowed to warm slowly to rt (~1 h). The reaction mixture was then cooled to −10 °C, treated with 100 mL of 10% KH_2PO_4, and acidified to pH 2 at ice-bath temperature. The aqueous layer was extracted with 3 × 100 mL of Et_2O, and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a dark residue. Chromatography (silica gel, 70:30:1 hexanes/EtOAc/HOAc) then afforded 0.8 g (51%) of **19** as a pale yellow solid. Recrystallization from EtOAc/hexanes gave **19** as colorless crystals: mp 82−3 °C; R_f 0.2 (90:10:1 hexanes/EtOAc/AcOH); MS m/z 156 (M^+); IR (KBr) 3300−2550 br, 2248, 1725, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.7 (s, 4H), 3.78 (s, 3H), 10.51 (br s, 1H). Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.75; H, 5.22.

1-((5′-Carbomethoxy-4′-pentynoyl)amino)-1*H*-pyrrole (20a). A solution of 308 mg (3.68 mmol) of *N*-aminopyrrole **17a** and 705 mg (4.50 mmol, 1.22 equiv) of acetylenic acid **19** in 2.0 mL of anhydrous THF was treated with 863 mg (4.50 mmol, 1.22 equiv) of EDCI, and the resulting mixture was stirred vigorously at rt for 5 h. At the end of this period the reaction mixture was concentrated and partitioned between H_2O and CH_2Cl_2, and the aqueous layer was extracted with 3 × 30 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a light yellow solid. Chromatography (silica gel, 30% EtOAc/hexanes) then gave 666 mg (82%) of **20a** as a 1:1 mixture of amide rotomers, which had mp 77−8 °C (colorless needles) following crystallization from CH_2Cl_2/hexanes: R_f 0.14 (30% EtOAc/hexanes); MS m/z 220 (M^+); IR ($CHCl_3$) 3232, 3032, 2945, 2244, 1704, 1681, 1535, 1436 cm^{-1}; ^{1}H NMR (rotomer 1), ($CDCl_3$) δ 2.32 (t, 2H, J = 8.37 Hz), 2.62 (t, 2H, J = 8.37 Hz), 3.73 (s, 3H), 6.18 (m, 2H), 6.69 (m, 2H), 8.00 (s, 1H); (rotomer 2) ($CDCl_3$) δ 2.55 (t, 2H, J = 8.37 Hz), 2.75 (t, 2H, J = 8.37 Hz), 3.76 (s, 3H), 6.18 (m, 2H), 6.64 (m, 2H), 8.29 (s, 1H). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 59.92; H, 5.49; N, 12.70.

2-((5′-Carbomethoxy-4′-pentynoyl)amino)-4,5,6,7-tetrahydro-2*H*-isoindole (20b). This material was prepared in a fashion identical to that for **20a** described above, using 200 mg (1.47 mmol) of *N*-aminopyrrole **17b**, 468 mg (3.0 mmol) of acetylenic acid **19**, and 575 mg (3.0 mmol) of EDCI in 2.0 mL of anhydrous THF. After the mixture was stirred for a total of 12 h, workup and purification as described for **20a** afforded 321 mg (80%) of **20b** as a colorless solid: mp 220−1°C (1:1 mixture of amide rotomers); R_f 0.20 (30% EtOAc/hexanes); MS m/z 274 (M^+); IR ($CHCl_3$) 3452, 3032, 2932, 2238, 1732, 1648, 1374, 1248 cm^1; ^{1}H NMR (combined rotomers) ($CDCl_3$) δ 1.66 (br s, 8H), 2.24−2.74 (br m, 16H), 3.72 (s, 6H), 6.28 (br d, 4H), 8.24 (br s, 1H), 9.04 (br s, 1H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.70; H, 6.60; N, 10.20. Found: C, 65.74; H, 6.63; N, 10.18.

1-((5′-Carbomethoxy-4′-pentynoyl)amino)-2-carbomethoxy-1*H*-pyrrole (21a). This material was prepared in a fashion identical to that for **20a** described above, using 100 mg (0.70 mmol) of *N*-aminopyrrole **18a**, 122 mg (0.78 mmol, 1.1 equiv) of acetylenic acid **19**, and 150 mg (0.78 mmol, 1.1 equiv) of EDCI in 2.0 mL of anhydrous THF. After the mixture was stirred for a total of 24 h, workup and purification as described for **20a** afforded 123 mg (63%) of **21a** as a colorless solid: mp 100−1 °C (55:45 mixture of amide rotomers); R_f 0.63 (90% Et_2O/petroleum ether); MS m/z 278 (M^+); IR ($CHCl_3$) 3392, 3032, 2952, 2244, 2768, 1712, 1444, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.51−2.94 (m, 8H), 3.73 (s, 3.3H), 3.76 (s, 2.7H), 6.14 (m, 0.55H), 6.17 (m, 0.45H), 6.62 (m, 0.45H), 6.67 (m, 0.55H), 6.90 (m, 0.45H), 6.95 (m, 0.55H), 8.40 (br s, 0.45H), 8.91 (br s, 0.55H). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.00; H, 5.08; N, 9.99.

1-Carbomethoxy-2-((5′-carbomethoxy-4′-pentynoyl)-amino-4,5,6,7-tetrahydro-2*H*-isoindole (21b). This material was prepared in a fashion identical to that for **20a** described above, using 80 mg (0.41 mmol) of *N*-aminopyrrole **18b**, 142 mg (0.91 mmol, 2.2 equiv) of acetylenic acid **19**, and 188 mg (0.91 mmol, 2.2 equiv) of DCC in 5.0 mL of anhydrous THF. After the mixture was stirred for a total of 12 h, workup and purification as described for **20a** afforded 108 mg (80%) of **21b** as a colorless solid: mp 115−16 °C (single amide rotomer); R_f 0.20 (30% EtOAc/hexanes); MS m/z 332 (M^+); IR (KBr) 3272, 3008, 2945, 2238, 1728, 1701, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (br s, 4H), 2.40 (m, 2H), 2.55 (m, 2H), 2.65 (m, 4H), 3.63 (s, 3H), 3.65 (s, 3H), 6.60 (s, 1H), 8.56 (br s, 1H). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 6.06; H, 61.43; N, 8.43. Found: C, 6.10; H, 61.45; N, 8.38.

***N*-Pyrrolo Enamides 22a.** A solution of 300 mg (1.36 mmol) of hydrazide **20a** in 50 mL of anhydrous DMF was heated to 80 °C in an oil bath for a period of 3 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 70% Et_2O/petroleum ether) to afford 221 mg (1.00 mmol) of *E*-**22a** and 76 mg (0.36 mmol) of *Z*-**22a** for a total yield of 99%. Crystallization from EtOAc yielded each isomer as colorless crystals. ***E*-22a**: mp 128−9 °C; R_f 0.25 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3032, 2945, 1705, 1645, 1438, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.74 (m, 2H), 3.37 (m, 2H), 3.65 (s,

3H), 4.90 (t, 1H, J = 2.0 Hz), 6.31 (t, 2H, J = 2.5 Hz), 6.60 (t, 2H, J = 2.5 Hz). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 60.01; H, 5.54; N, 12.65. ***Z*-22a**: R_f 0.20 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3025, 2945, 1765, 1715, 1228, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (m, 2H), 2.92 (m, 2H), 3.32 (s, 3H), 5.09 (s, 1H), 6.22 (m, 2H), 6.64 (m, 2H). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 60.08; H, 5.55; N, 12.67.

***N*-Pyrrolo Enamides 22b.** A solution of 320 mg (1.17 mmol) of hydrazide **20b** in 20 mL of anhydrous DMF was heated to 80 °C in an oil bath for a period of 2 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 70% CH_2Cl_2/EtOAc) to afford 200 mg (0.73 mmol) of ***E*-22b** and 98 mg (0.36 mmol) of ***Z*-22b** for a total yield of 93%. Crystallization yielded each isomer as colorless crystals. ***E*-22b**: mp 183−85 °C; R_f 0.70 (70% CH_2Cl_2/EtOAc); MS m/z 274 (M^+); IR ($CHCl_3$) 3019, 2932, 2852, 1708, 1648, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.54 (m, 4H), 2.71 (m, 2H), 3.33 (m, 2H), 3.67 (s, 3H), 4.96 (t, 1H, J = 2.0 Hz), 6.24 (s, 2H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.59; H, 6.64; N, 10.20. ***Z*-22b**: mp 153−54 °C; R_f 0.60 (70% CH_2Cl_2/EtOAc); MS m/z 274 (M^+); IR ($CHCl_3$) 3012, 2932, 2852, 1759, 1705, 1438, 1258, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 4H), 2.52 (m, 4H), 2.64 (m, 2H), 2.87 (m, 2H), 3.27 (s, 3H), 5.01 (s, 1H), 6.25 (s, 2H).

***N*-Pyrrolo Enamides 23a.** A solution of 342 mg (1.23 mmol) of hydrazide **21a** in 60 mL of anhydrous DMF was heated to 80 °C in an oil bath for a period of 2 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 30% EtOAc/hexanes) to afford 233 mg (0.84 mmol) of ***E*-23a** and 94 mg (0.34 mmol) of ***Z*-23a** for a total yield of 94%. Crystallization from $CHCl_3$/hexanes yielded each isomer as colorless crystals. ***E*-23a**: mp 109−10 °C; R_f 0.66 (90% Et_2O/petroleum ether); MS m/z 278 (M^+); IR ($CHCl_3$) 3032, 2945, 1765, 1708, 1648, 1445, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (m, 2H), 3.29 (m, 1H), 3.49 (m, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 4.70 (t, 1H, J = 2.0 Hz), 6.33 (m, 1H), 6.83 (m, 1H), 7.05 (m, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.15; H, 5.14; N, 10.00. ***Z*-23a**: mp 90−1 °C; R_f 0.44 (90% Et_2O/petroleum ether); MS m/z 278 (M^+); IR ($CHCl_3$) 3032, 3012, 2945, 1765, 1715, 1662, 1198, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71 (m, 2H), 2.91 (m, 1H), 3.05 (m, 1H), 3.34 (s, 3H), 3.75 (s, 2H), 5.09 (t, 1H, J = 2.0 Hz), 6.26 (m, 1H), 6.93 (m, 1H), 6.99 (m, 1H).

***N*-Pyrrolo Enamides 23b.** A solution of 30 mg (0.09 mmol) of hydrazide **21b** in 20 mL of anhydrous DMF was heated to 80 °C in an oil bath for a period of 2 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 30% EtOAc/hexanes) to afford 22 mg (0.07 mmol) of ***E*-23b** and 7 mg (0.02 mmol) of ***Z*-23b** for a total yield of 97%. Crystallization yielded each isomer as colorless crystals. ***E*-23b**: mp 107−8 °C; R_f 0.80 (70:15:15 CH_2Cl_2/EtOAc/hexanes); MS m/z 332 (M^+); IR ($CHCl_3$) 3032, 1762, 1702, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H); 2.51 (m, 2H), 2.68 (m, 1H), 2.77 (m, 2H), 2.80 (m, 1H), 3.26 (m, 1H), 3.45 (m, 1H), 3.64 (s, 3H), 3.71 (s, 3H), 4.73 (t, 1H, J = 2.5 Hz), 6.50 (s, 1H). ***Z*-23b**: mp 112−3 °C; R_f 0.7 (70:15:15 CH_2Cl_2/EtOAc/hexanes); MS m/z 332 (M^+); IR ($CHCl_3$) 3019, 1765, 1702, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (m, 4H), 2.52 (m, 2H), 2.66 (m, 1H), 2.72 (m, 1H), 2.75 (m, 2H), 2.86 (m, 1H), 3.01 (m, 1H), 3.28 (s, 3H), 3.72 (s, 3H), 5.03 (s, 1H), 6.59 (s, 1H). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.45; H, 6.10; N, 8.38. Found: C, 61.50; H, 6.12; N, 8.39.

General Conditions for Photolysis. All photolyses were carried out in a Rayonet photochemical reactor at 300 nm, employing 7×10^{-3} M solutions of substrate in *tert*-amyl alcohol. Piperylene was added to a concentraton of 1 M. Reaction solutions were purged with argon for 30 min and then cooled to constant T = −10 °C (maintained by thermostat). The reaction was monitored by TLC for a period of 10−48 h (T = −10 °C, under argon) and was purified by preparative TLC, Chromatotron, or flash chromatography.

Photolysis of *N*-Pyrrolo Enamide 22a (→ 24a, 28a, 30). Photolysis of *N*-pyrrolo enamide **22a** by following the general procedure described above afforded 40−50% of **24a** as a 1:1 E/Z mixture, 15−20% of **28a** as a 1:1 E/Z mixture, and 0−5% of **30** as a 1:1 E/Z mixture. Purification was accomplished by preparative TLC and crystallization from $CHCl_3$/hexanes.

***E*-24a**: mp 174−5 °C; R_f 0.16 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3666, 3473, 3386, 3025, 3005, 2945, 1752, 1692, 1628, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 3.35 (m, 2H) 3.73 (s, 3H), 6.11 (m, 1H), 6.22 (m, 1H), 6.79 (m, 1H), 8.09 (br s, 1H), 8.66 (br s, 1H).

***Z*-24a**: mp 176−7 °C; R_f 0.27 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3479, 3332, 3025, 3005, 2952, 1748, 1685, 1618, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (m, 2H), 2.95 (m, 2H), 3.75 (s, 3H), 6.05 (m, 1H), 6.21 (m, 1H), 6.79 (m, 1H), 8.49 (br s, 1H), 10.27 (br s, 1H). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 60.02; H, 5.52; N, 12.66.

***E*-28a**: mp 119−20 °C; R_f 0.19 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3466, 3005, 2952, 1705, 1632, 1194, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (m, 2H), 3.33 (m, 2H), 3.65 (s, 3H), 5.37 (t, 1H, J = 2 Hz), 6.10 (m, 1H), 6.24 (m, 1H), 6.73 (m, 1H), 8.59 (br s, 1H). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 60.04; H, 5.51; N, 12.65.

***Z*-28a**: oil; R_f 0.12 (70% Et_2O/petroleum ether); MS m/z 220 (M^+); IR ($CHCl_3$) 3466, 3025, 2938, 1705, 1655, 1575, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (t, 2H, J = 8.50 Hz), 2.90 (t, 2H, J = 8.50 Hz), 3.31 (s, 3H), 5.09 (s, 1H), 5.90 (s, 1H), 6.17 (d, 1H, J = 2.75 Hz), 6.71 (s, 1H), 8.41 (br s, 1H).

***E*-30**: mp 141−2 °C; R_f 0.50 (30% EtOAc/CH_2Cl_2); MS m/z 155 (M^+); IR ($CHCl_3$) 3412, 3039, 2552, 1728, 1708, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (m, 2H), 3.29 (m, 2H), 3.68 (s, 3H), 5.29 (t, 1H, J = 2 Hz), 7.43 (br s, 1H).

***Z*-30**: oil; R_f 0.30 (30% EtOAc/CH_2Cl_2); MS m/z 155 (M^+); IR ($CHCl_3$) 3419, 3025, 2932, 1732, 1641, 1448, 1374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (m, 2H), 2.86 (m, 2H), 3.69 (s, 3H), 4.98 (t, 1H, J = 1.50 Hz), 9.76 (br s, 1H).

Photolysis of *N*-Pyrrolo Enamide 22b (→ 24b, 26b, 28b, 30). Photolysis of *N*-Pyrrolo enamide **22b** by following the general procedure described above afforded 40−50% of **24b** as a 1:1 E/Z mixture, 15−20% of **26b** as a 1:1 E/Z mixture, 5−10% of **28b** as a 1:1 E/Z mixture, and 0−5% of **30** as a 1:1 E/Z mixture. Purification was accomplished by preparative TLC and crystallization from EtOAc/hexanes.

***E*-24b**: mp 200−1 °C; R_f 0.18 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3473, 3379, 3025, 2932, 2852, 1728, 1621, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.26 (m, 2H), 2.57 (m, 2H), 2.62 (m, 2H), 3.37 (m, 2H), 3.68 (s, 3H), 6.52 (s, 1H), 7.44 (br s, 1H), 7.84 (br s, 1H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.26; H, 6.63; N, 10.08.

***Z*-24b**: mp 173−4 °C; R_f 0.24 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3412, 3025, 2845, 1715, 1695, 1438, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.32 (m, 2H), 2.47 (m, 2H), 2.59 (m, 2H), 2.69 (m, 2H), 3.69 (s, 3H), 6.50 (s, 1H), 7.69 (br s, 1H), 10.29 (br s, 1H);

***E*-26b:** mp 208−9 °C; R_f 0.24 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3466, 3025, 2932, 2852, 1742, 1702, 1635, 1438, 1221, 1147 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (m, 4H), 2.25 (m, 2H), 2.55 (m, 2H), 2.68 (m, 2H), 3.32 (m, 2H), 3.64 (s, 3H), 5.09 (s, 1H), 6.46 (s, 1H), 7.69 (br s, 1H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.70; H, 6.66; N, 10.04.

***Z*-26b**: oil; R_f 0.10 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3466, 3006, 2932, 1718, 1635, 1438, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (m, 4H), 2.20 (m, 2H), 2.52 (t, 2H, J = 6.50 Hz), 2.63 (t, 2H, J = 6.50 Hz), 2.82 (m, 1H), 2.89 (m, 1H), 3.30 (s, 3H), 5.05 (s, 1H), 6.44 (d, 1H, J = 2.50 Hz), 7.87 (br s, 1H).

***E*-28b**: mp 166−67 °C; R_f 0.34 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3386, 3026, 2932, 2852, 1728, 1708, 1635, 1438, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.56 (m, 4H), 2.63 (m, 2H), 3.37 (m, 2H), 3.72 (s, 3H), 6.18 (s, 2H), 7.16 (br s, 1H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.59; H, 6.65; N, 10.17.

***Z*-28b**: mp 171−2 °C; R_f 0.34 (50% Et_2O/petroleum ether); MS m/z 274 (M^+); IR ($CHCl_3$) 3473, 3012, 2932, 2852, 1748,

1728, 1682, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.46 (m, 2H), 2.54 (br s, 4H), 2.74 (m, 2H), 3.70 (s, 3H), 6.17 (s, 2H), 9.85 (br s, 1H).

Photolysis of *N*-Pyrrolo Enamide 23a (→ 25a, 29a, 30). Photolysis of *N*-pyrrolo enamide **23a** by following the general procedure described above afforded 40−50% of **25a** as a 1:1 *E*/*Z* mixture, 15−20% of **29a** as a 1:1 *E*/*Z* mixture, and 0−5% of **30** as a 1:1 *E*/*Z* mixture. Purification was accomplished by preparative TLC and crystallization from $CHCl_3$/hexanes.

***E*-25a**: mp 217−8 °C; R_f 0.25 (90% Et_2O/petroleum ether); MS *m*/*z* 278 (M^+); IR ($CHCl_3$) 3446, 3393, 3032, 2999, 1728, 1702, 1621, 1264, 1194 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (m, 2H), 3.38 (m, 2H), 3.72 (s, 3H), 3.82 (s, 3H), 6.14 (m, 1H), 6.88 (m, 1H), 8.05 (br s, 1H), 9.55 (br s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.39; H, 5.11; N, 9.81.

***Z*-25a**: mp 189−90 °C; R_f 0.36 (90% Et_2O/petroleum ether); MS *m*/*z* 278 (M^+); IR ($CHCl_3$) 3439, 3319, 3025, 2945, 1752, 1704, 1635, 1491, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (m, 2H), 2.93 (m, 2H), 3.75 (s, 3H), 3.85 (s, 3H), 6.10 (m, 1H), 6.88 (m, 1H), 9.29 (br s, 1H), 10.35 (br s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.95; H, 5.09; N, 9.96.

***E*-29a**: mp 194−5 °C; R_f 0.39 (90% Et_2O/petroleum ether); MS *m*/*z* 278 (M^+); IR ($CHCl_3$) 3439, 3025, 2952, 1742, 1705, 1635, 1491, 1224, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (m, 2H), 3.37 (m, 2H), 3.66 (s, 3H), 3.83 (s, 3H), 5.44 (t, 1H, J = 2.0 Hz), 6.16 (m, 1H), 6.93 (m, 1H), 9.32 (br s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.05; H, 5.12; N, 10.04.

***Z*-29a**: mp 135−6 °C; R_f 0.15 (90% Et_2O/petroleum ether); MS *m*/*z* 278 (M^+); IR ($CHCl_3$) 3459, 3032, 2952, 1718, 1704, 1648, 1444 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (m, 2H), 2.92 (m, 2H), 3.30 (s, 3H), 3.79 (s, 3H), 5.05 (t, 1H, J = 2.00 Hz), 6.24 (t, 1H, J = 2.50 Hz), 6.92 (t, 1H, J = 2.50 Hz), 9.06 (br s, 1H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.59; H, 6.65; N, 10.17.

Photolysis of *N*-Pyrrolo Enamide 23b (→ 25b, 27b, 32). Photolysis of *N*-pyrrolo enamide **23b** following the general procedure described above afforded 40−50% of **25b** as a 1:1 *E*/*Z* mixture, 5−10% of **27b** as a 1:1 *E*/*Z* mixture, and 0−5% of **32**. Purification was accomplished by preparative TLC and crystallization from EtOAc/hexanes.

***E*-25b**: mp 214−5 °C; R_f 0.3 (silica gel, 70:15:15 CH_2Cl_2/EtOAc/hexanes); MS *m*/*z* 332 (M^+); IR ($CHCl_3$) 3452, 3386, 3025, 2936, 2858, 1755, 1698, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.22 (t, 2H, J = 6.0 Hz), 2.62 (m, 2H), 2.78 (t, 2H, J = 6.0 Hz), 3.39 (m, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 7.40 (br s, 1H), 8.75 (br s, 1H). Structure confirmed by X-ray analysis.[22] Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 61.14; H, 6.12; N, 8.37.

***Z*-25b**: mp 208−9 °C; R_f = 0.34 (70% CH_2Cl_2/EtOAc); MS *m*/*z* 332 (M^+); IR ($CHCl_3$) 3453, 3332, 3012, 2945, 1752, 1685, 1625, 1278, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.27 (t, 2H, J = 6.0 Hz), 2.49 (m, 2H), 2.68 (m, 2H), 2.79 (t, 2H, J = 6.0 Hz), 3.67 (s, 3H), 3.80 (s, 3H), 8.57 (br s, 1H), 10.32 (br s, 1H).

***E*-27b**: mp 166−7 °C; R_f 0.29 (70% CH_2Cl_2/EtOAc); MS *m*/*z* 332 (M^+); IR ($CHCl_3$) 3394, 2941, 1730, 1693, 1648, 1443, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.50 (m, 2H), 2.62 (t, 2H, J = 7.50 Hz), 2.79 (m, 2H), 3.34 (m, 1H), 3.49 (m, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 6.40 (s, 1H), 6.90 (br s, 1H).

***Z*-27b**: mp 200−1 °C; R_f 0.34 (70% CH_2Cl_2/EtOAc); MS *m*/*z* 332 (M^+); IR ($CHCl_3$) 3406, 3008, 2947, 1717, 1711, 1705, 1363, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.46 (m, 2H), 2.52 (m, 2H), 2.55 (m, 1H), 2.67 (m, 1H), 2.80 (m, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 6.41 (s, 1H), 9.85 (br s, 1H). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 60.88; H, 6.09; N, 8.33.

32: mp 94−5 °C (colorless crystals); R_f 0.80 (70% CH_2Cl_2/EtOAc); MS *m*/*z* 179 (M^+); IR ($CHCl_3$) 3459, 3019, 2939, 2852, 1685, 1458, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.51 (t, 2H, J = 6.0 Hz), 2.77 (t, 2H, J = 6.0 Hz), 3.80 (s, 3H), 6.62 (d, 1H, J = 2.5 Hz), 8.74 (br s, 1H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.11; H, 7.32; N, 7.82.

***d,l*-1-(Trimethylsilyl)-3-methoxy-1-butyne, Hexacarbonyldicobaltate Complex (42)**. The procedure of Schreiber *et al.*[18a] was modified as follows. A solution of 10.0 g (119 mmol) of *d,l*-3-methoxy-1-butyne in 100 mL of anhydrous THF was cooled to −78 °C under argon and was treated in a dropwise fashion, with vigorous stirring, with 48 mL (120 mmol) of 2.5 M *n*-BuLi/hexane. After the addition was complete, the reaction mixture was stirred for an additional 30 min at −78 °C and then the reaction was quenched with 19.0 mL (149 mmol) of trimethylsilyl chloride (TMSCl). Stirring was continued for 8 h at −78 °C and then for 2 h at rt before the mixture was poured over 100 g of crushed ice. After melting, the aqueous layer was extracted with 3 × 35 mL of Et_2O and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a colorless oil. Distillation under reduced pressure then gave 17.98 g (96%) of *d,l*-1-(trimethylsilyl)-3-methoxy-1-butyne as a clear, colorless oil, $bp_{1.0}$ 27 °C. This last material was converted into its hexacarbonyl dicobaltate derivative **42** as follows. A total of 4.72 g (13.8 mmol) of octacarbonyldicobalt was weighed into a 100 mL flask in a dry box and dissolved in 20 mL of Et_2O which was thoroughly purged with argon. A solution of 2.16 g (13.8 mmol) of *d,l*-1-(trimethylsilyl)-3-methoxy-1-butyne in 20 mL Et_2O was then added in a dropwise fashion, with vigorous stirring, over a period of 15 min (brisk evolution of CO is observed). After the addition was complete, stirring was continued for 40 min, at which point the solvent was evaporated under reduced pressure to afford 6.9 g of a red gum. Chromatography (silica gel, 5% EtOAc/hexanes) then gave 5.54 g (96%) of **42** as a red oil which was used as such in subsequent steps.

General Procedure for Nicholas−Schreiber Condensations. A solution of 35−50 mmol (1.0 equiv) of Bu_2BOTf in 60 mL of CH_2Cl_2 was cooled to 0 °C under argon and was treated in a dropwise fashion, with vigorous stirring, with 1.0 equiv of diisopropylethylamine. The resulting yellow solution was stirred for an additional 30 min at 0 °C before being treated with 1.0 equiv of the appropriate chiral auxiliary **41** or **48** in CH_2Cl_2 and cooled to −78 °C. An additional 1.0 equiv of 1 M Bu_2BOTf/CH_2Cl_2 was then added *via* syringe, followed by a solution of 0.56 equiv of the appropriate cobalt complex in 80 mL of CH_2Cl_2. The resulting dark red solution was stirred at −78 °C for 30 min, and at 0 °C for an additional 30 min, before being allowed to slowly warm to rt. At this point the reaction mixture was followed by TLC and was generally complete within 20−30 min at rt depending upon the scale. The reaction was quenched with phosphate buffer to pH 7, and the aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined extracts were washed with 10 mL of H_2O, dried over Na_2SO_4, and filtered through a short column of silica gel contained in a fritted glass funnel (4.5 × 6 cm^2 with 0.5 cm of Celite on top). The filtrate was concentrated under reduced pressure to give a dark red oil, which was purified by chromatography on silica gel (10% EtOAc/hexanes) to give a red-black solid which was used immediately for the next step. A 1.0 M solution of the Nicholas adduct cobalt complex in acetone was treated in small portions, and with vigorous stirring, with solid ceric ammonium nitrate (CAN) such that each aliquot was added as soon as the effervescence due to the previous addition of CAN ceased. Addition was continued until no more effervescence was evident (a large excess of CAN should be avoided). The resulting yellow solution was stirred for an additional 15 min at rt (total ∼40 min) before being concentrated under reduced pressure. The residue was partitioned between 100 mL of H_2O and Et_2O, and the aqueous layer was extracted with 3 × 30 mL of Et_2O. The combined extracts were washed with 10 mL of saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by chromatography.

Nicholas Adduct 53. This material was prepared in 94% yield from 6.1 g (32.6 mmol) of oxazolidinone **48** and 8.0 g (18.1 mmol) of cobalt complex **42** by following the general procedure described above. Chromatography (silica gel, 15% EtOAc/hexanes) followed by crystallization (pentanes) afforded 5.26 g (94%) of **53** as a colorless solid: mp 82−3 °C; R_f 0.43 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 20.65° (*c* 28.46, MeOH); IR (CH_2Cl_2)

2940, 2858, 2253, 1745, 1697, 1575, 1605, 1455, 1402, 1308, 1241, 1189, 1102, 958, 911, 829, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.072 (s, 9H), 0.91 (m, 6H), 1.16 (m, 6H), 2.36 (m, 1H), 2.89 (dq, J = 7.5 Hz, 1H), 3.91 (dq, J =7.5 Hz, 1H), 4.24 (m, 2H), 4.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.97, 153.37, 109.39, 84.69, 62.99, 58.25, 42.51, 28.97, 28.35, 17.83, 16.95, 14.79, 13.89, 0.006 ($SiMe_3$). Anal. Calcd for $C_{16}H_{27}O_3NSi$: C, 62.10; H, 8.79; N, 4.53. Found: C, 62.09; H, 8.83; N, 4.57.

2(*R*),3(*R*)-Dimethyl-4-pentynoic Acid (54a). A solution of 3.09 g (10.0 mmol) of Nicholas adduct **53** in 130 mL of 3:1 THF/H_2O was cooled to 0 °C with stirring and was treated sequentially with 60 mL (30.0 mmol) of 0.50 M LiOH followed by 9.06 mL (80.0 mmol) of 30% H_2O_2. Stirring was continued at 0 °C for 1 h and then at rt for 2 h, at which point TLC analysis showed no more starting material. The reaction mixture was then cooled to 0 °C and the reaction quenched by the addition of a solution of 10.08 g (80.0 mmol) of Na_2SO_3 in 50 mL of H_2O (CAUTION: this reaction is highly exothermic). After the reaction mixture was stirred for 30 min at rt, a solution of 10 mL of saturated $NaHCO_3$ was added and the aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to recover 1.21 g of the chiral auxiliary. The aqueous layer was cooled and acidified with concd HCl to pH 2 and extracted with 3 × 20 mL of EtOAc. The combined extracts were washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to give 1.06 g (92%) of acid **54a** as a clear, colorless liquid: $bp_{0.75}$ 35 °C; R_f 0.6 (7:2:1 hexane/EtOAc/HOAc); $[\alpha]^{25}_D$ = 4.77° (*c* 13.85, MeOH); IR (film) 3301, 2982, 2841, 2360, 1710, 1643, 1457, 1416, 1384, 1269, 1232, 1138, 1067, 844, 778, 629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 7.08 Hz, 3H), 1.23 (d, J = 7.16 Hz, 3H), 2.11 (d, J = 2.1 Hz, 1H), 2.64 (dq, J = 6.7 Hz, 1H), 2.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 181.03, 86.10, 69.70, 44.07, 28.14, 16.87, 12.93; MS (EIMS) *m*/*z* 126 (M^+). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.93. Found: C, 66.06; H, 7.93.

2(*S*),3(*S*)-Dimethyl-4-pentynoic Acid (*ent*-54a). This material was prepared in 92% yield from 1.02 g (2.97 mmol) of Nicholas adduct **44s**[18a] by following an identical procedure as described above for **54a**. Distillation gave 347 mg (92%) of *ent*-**54a** as a clear, colorless liquid, $bp_{0.75}$ 35 °C, having spectral data identical to those of **54a**; $[\alpha]^{25}_D$ = −4.80° (*c* 14.99, MeOH).

1-Carbomethoxy-2-((2'(*R*),3'(*R*)-dimethyl-5'-carbomethoxy-4'-pentynoyl)amino)-4,5,6,7-tetrahydro-2*H*-isoindole (55a). This material was prepared in a fashion identical to that for hydrazide **20a** described above, using 200 mg (1.59 mmol) of acetylenic acid **54a**, 308 mg (1.59 mmol) of *N*-aminopyrrole **18b** in 25 mL of anhydrous THF, and 785 mg (3.97 mmol) of EDCI, which was stirred for 72 h at rt. Purification by flash chromatography (silica gel, 15% EtOAc/hexanes) gave 441 mg (92%) of **55a** as a white microcrystalline solid: mp 139−40 °C (EtOAc/hexanes); R_f 0.4 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 26.16° (*c* 3.02, MeOH); IR (KBr) 3284, 2983, 1674, 1572, 1516, 1449, 1410, 1375, 1325, 1264, 1243, 1148, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.96 Hz, 3H), 1.33 (d, J = 7 Hz, 3H), 1.72 (m, 4H), 2.17 (d, J = 2.4 Hz, 1H), 2.53 (m, 2H), 2.55 (dq, 1H), 2.76 (m, 2H), 2.88 (m, 1H), 3.79 (s, 3H), 6.78 (s, 1H), 9.07 (br s, 1H); MS (EIMS) *m*/*z* 302 ($M^{+\bullet}$). Anal. Calcd for $C_{17}H_{22}O_3N_2$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.45; H, 7.37; N, 9.22.

1-Carbomethoxy-2-((2'(*S*),3'(*S*)-dimethyl-5'-carbomethoxy-4'-pentynoyl)amino)-4,5,6,7-tetrahydro-2*H*-isoindole (*ent*-55a). This material was prepared in 94% yield from 584 mg (4.64 mmol) of acetylenic acid *ent*-**54a**, 900 mg (4.64 mmol) of *N*-aminopyrrole **18b** in 50 mL of anhydrous THF, and 1.6 g (8.3 mmol) of EDCI, which was stirred for 72 h at rt. Flash chromatography (silica gel, 15% EtOAc/hexanes) gave 1.33 g (94%) of *ent*-**55a** as a white microcrystalline solid: mp 139−40 °C, having spectral data identical to those of **55a**; $[\alpha]^{25}_D$ = −26.01° (*c* 4.54, MeOH).

***N*-Pyrrolo Enamide 56a. Method A.** A solution of 101 mg (0.33 mmol) of hydrazide **55a** in 20 mL of absolute methanol was treated with 81.5 mg (0.99 mmol) of NaOAc and 10.1 mg (cat.) of $PdCl_2(CH_3CN)_2$. The reaction mixture was then fitted with a reflux condenser and repeatedly degassed by being purged with argon and evacuated through a two-way adapter. The degassed mixture was then heated at reflux for a period of 3 h, at which point TLC analysis showed complete disappearance of starting material. The catalyst was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give a honey-colored gum. Purification by preparative TLC (500 μm, silica gel, 30% EtOAc/hexanes) then afforded 71.1 mg (71%) of **56a** as a pale yellow gum which solidified in the freezer: R_f 0.72 (13:4:2:1 hexanes/benzene/EtOAc/MeOH); $[\alpha]^{25}_D$ = 16.32° (*c* 5.98, MeOH); IR (CH_2Cl_2) 3049, 2937, 2858, 2304, 1742, 1701, 1576, 1505, 1455, 1402, 1303, 1241, 1146, 1095, 1027, 966, 902, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ (two atropisomers) 1.30−1.35 (m, 6H), 1.71 (m, 4H), 2.21 (dq, J = 4 Hz, J = 7.2 Hz, 1H), 2.39 (dq, J = 7.5 Hz, J = 4 Hz, 1H), 2.50 (m, 2H), 2.78 (m, 2H), 3.71, 3.70 (2s, 3H), 3.79, 3.86, 4.10, 4.14 (4 sets of t, J = 2 Hz, 2H), 6.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (two atropisomers) 174.28 (174.62), 160.15 (160.199), 152.10 (152.17), 129.87 (129.95), 124.52 (124.54), 120.00 (120.01), 82.23 (82.88), 50.87 (50.92), 42.06 (42.82), 38.48 (39.28), 23.74 (23.80), 22.08, 17.19 (17.67), 14.50 (14.95); MS (EIMS) *m*/*z* 302 ($M^{+\bullet}$).

***N*-Pyrrolo Enamide *ent*-56a. Method B.** A solution of 604 mg (2.0 mmol) of hydrazide *ent*-**55a** in 60 mL of THF was treated with 6.0 mL (6.0 mmol) of 1.0 M *n*-Bu_4NF (TBAF) in THF, and the solution was repeatedly degassed by being purged with argon and evacuated through a two-way adapter. The reaction was then heated to reflux for 1 h under an atmosphere of argon, cooled to rt, and concentrated under reduced pressure. The residue was suspended in 10 mL of water and extracted with 3 × 10 mL of CH_2Cl_2. The combined extracts were washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to give a pale yellow gum. Purification by preparative TLC (2000 μm, silica gel GF, 30% EtOAc/hexanes) then afforded 435 mg (72%) of *ent*-**56a** as a glassy gum which slowly solidified in the freezer. This compound had identical TLC behavior and spectral data as that for **56a** above (two atropisomers); $[\alpha]^{25}_D$ = −16.42° (*c* 23.93, MeOH).

1-(Trimethylsilyl)-3(*R,*S**)-4(*S*)-dimethoxy-1-pentyne (59b).** A solution of lithium(trimethylsilyl)acetylide (LiTMSA) in THF/hexanes was prepared from 5.11 g (79.9 mmol) of (trimethylsilyl)acetylene in 100 mL of anhydrous THF and 31.99 mL (79.9 mmol) of 2.5 M *n*-BuLi/hexanes, which was cooled to −78 °C under nitrogen with vigorous stirring (inverse addition over 20 min). This solution was then treated at −78 °C with 6.4 g (72.2 mmol) of aldehyde **57b**, and after the solution was stirred for 15 min, 12.09 g (95.9 mmol) of Me_2SO_4 was added over a period of 20−30 min. The reaction mixture was then allowed to warm slowly to rt (2−4 h), and stirring was continued at rt for 8 h. At the end of this period, the reaction mixture was quenched by pouring the mixture over 100 g of crushed ice and the aqueous phase was extracted with 4 × 20 mL of Et_2O. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 11.7 g of a pale yellow oil. Flash chromatography (silica gel, 5% EtOAc/hexanes) then gave 6.95 g (48%) of **59b** as a colorless oil: $bp_{0.75}$ 45 °C R_f 0.78 (50% EtOAc/hexanes); $[\alpha]^{25}_D$ = −22.48° (*c* 16.55, MeOH); IR (film) 3360, 2933, 2899, 2823, 2172, 1100, 1012, 976, 848 cm^{-1}; ^1H NMR ($CDCl_3$) δ (two diastereomers) 0.18 (s, 9H), 1.23 (d, J = 8 Hz, 3H), 3.40, 3.43, 3.45 (3s, 6H total), 3.95 (d, J = 6Hz, 1H) 4.04 (d, 1H); MS (EIMS) *m*/*z* 200 ($M^{+\bullet}$). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.78, H, 10.06.

1-(Trimethylsilyl)-3-(*RS*)-methoxy-4(*S*)-(benzyloxy)-1-pentyne (59c).** This material was prepared in a fashion identical to that for **59b** described above, using 15.6 mL (25.0 mmol) of 1.6 M *n*-BuLi/hexanes, 2.5 g (25.0 mmol) of (trimethylsilyl)acetylene in 60 mL of anhydrous THF, 4.1 g (25.0 mmol) of aldehyde **57c** in 50 mL of THF, and 3.8 g (28.5 mmol) of Me_2SO_4. Flash chromatography (silica gel, 5% EtOAc/hexanes) gave 6.5 g (94%) of **59c** as a colorless oil: $bp_{0.75}$ 60 °C; R_f 0.77 (20% EtOAc/hexanes); $[\alpha]^{25}_D$ = −22.80° (*c* 11.8, MeOH), IR (film) 2960, 2898, 2823, 2171, 1453, 1374, 1313, 1250,1196, 1104, 1027, 843, 760, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ (most polar diastereomer) 0.19 (s, 9H,), 1.28 (d, J = 6.36 Hz, 3H), 3.45 (s, 3H), 3.67 (m, 1H), 4.02 (d, 1H), 4.65 (q, J =

5.76 Hz, 2H), 7.33 (m, 5H); ^{1}H NMR ($CDCl_3$) δ (less polar diastereomer) 0.18 (s, 9H), 1.27(d, J = 6.28 Hz, 3H), 3.44 (s, 3H), 3.64 (m, 1H), 3.99 (d, 1H), 4.66 (q, J = 5.75 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 138.53, 128.24, 127.64, 127.45, 102.33, 91.87, 81.03, 76.59, 76.21, 74.76, 71.41, 57.09, 15.61, 0.107 ($SiMe_3$). Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.52; H, 8.75. Found: C, 69.65; H, 8.75.

1-(Trimethylsilyl)-3(*R*S)-4(*S*)-dimethoxy-1-pentyne, Hexacarbonyl Dicobaltate Complex (60b).** This material was prepared in a fashion identical to that for cobalt complex **42** described above, using 5.1 g (15 mmol) of octacarbonyldicobalt in 25 mL of Et_2O and 3.0 g (15 mmol) of alkyne **59b** in 75 mL of Et_2O. Flash chromatography (silica gel, 5% EtOAc/hexanes) gave 6.8 g (93%) of **60b** as a dark red oil.

1-(Trimethylsilyl)-3(*R*S)-methoxy-4(*S*)-benzyloxy-1-pentyne, Hexacarbonyl Dicobaltate Complex** (**60c**). This material was prepared in a fashion identical to that for cobalt complex **42** described above, using 11.4 g (33.5 mmol) of octacarbonyldicobalt in 125 mL of Et_2O and 9.3 g (33.5 mmol) of alkyne **59c** in 125 mL of Et_2O. Flash chromatography (silica gel, 5% EtOAc/hexanes) gave 18.5 g (97%) of **60c** as a dark red oil.

Nicholas Adduct 61b. This material was prepared in 96% yield from 4.46 g (24.08 mmol) of oxazolidinone **48** and 6.5 g (13.38 mmol) of cobalt complex **60b** following the general procedure described above. Chromatography (silica gel, 15% EtOAc/hexanes) followed by crystallization from pentane afforded 4.55 g (96%) of **61b** as colorless cubes: mp 106−7 °C; R_f 0.66 (50% EtOAc/hexanes); $[\alpha]^{25}_D$ = −34.01° (*c* 29.44, MeOH); IR (CH_2Cl_2) 2964, 2827, 2306, 2169, 1780, 1700, 1487, 1453, 1421, 1385, 1256, 1220, 1086, 1020, 844, 802 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9H), 0.93 (2d, J = 7.3 Hz, 6H), 1.18 (d, J = 7.3 Hz, 3H), 1.29 (d, J = 6.2 Hz, 3H), 2.4 (dt, J = 3.2 Hz, 6.2 Hz, 1H), 2.90 (d, J = 3.2 Hz, 1H), 3.33 (s, 3H), 3.53 (dq, J = 3.2 Hz, 6.2 Hz, 1H), 4.26 (m, 3H), 4.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 175.68, 153.30, 105.29, 87.45, 74.48, 63.02, 58.46, 56.36, 40.82, 39.58, 28.48, 17.95, 16.53, 15.61, 15.08, 0.078 ($SiMe_3$). Anal. Calcd for $C_{18}H_{31}O_4NSi$: C, 61.15; H, 8.84; N, 3.96. Found: C, 61.22; H, 8.88; N, 3.94.

Nicholas Adduct 61c. This material was prepared in 96% yield from 2.2 g (11.6 mmol) of oxazolidinone **48** and 3.3 g (5.8 mmol) of cobalt complex **60c** by following the general procedure described above. Chromatography (silica gel, 15% EtOAc/hexanes) afforded 2.4 g (96%) of **61c** as a colorless gum: R_f 0.64 (20% EtOAc/hexanes); $[\alpha]^{25}_D$ = −33.54° (*c* 4.8, MeOH); IR ($CDCl_3$) 2967, 2877, 2171, 1779, 1700, 1487, 1454, 1385, 1302, 1250, 1207 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.094 (s, 9H), 0.91 (d, J = 6.84 Hz, 6H), 1.03 (d, J = 6.84 Hz, 3H), 1.33 (d, J = 6.24 Hz, 3H), 2.38 (dt, 1H), 2.87 (dd, J = 3.08 Hz, 10.28 Hz, 1H), 3.70 (dq, 1H), 4.24 (m, 3H), 4.46 (d, J = 12.16 Hz, 1H), 4.47 (m, 1H), 4.66 (d, J = 12.16 Hz, 1H), 7.32 (m, 5H); MS (CIMS) *m*/*z* 430 (M + 1)$^+$; HRMS (CIMS) calcd for $C_{24}H_{35}O_4NSi$ 430.2398, found 430.2390; HRMS (EIMS) calcd 429.2398, found: 429.2336.

Nicholas−Schreiber Condensation of *ent*-60c and 41. Adduct *ent*-**41c** (Scheme 10, not shown) was prepared in 92% yield from 3.12 g (10.34 mmol) of oxazolidinone **41** and 2.90 g (5.17 mmol) of cobalt complex *ent*-**60c** by following the general procedure described above. Chromatography (silica gel, 15% EtOAc/hexanes) afforded 1.92 g (92%) of *ent*-**41c** as a glassy gum: R_f 0.68 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 11.32 (*c* 6.45, MeOH); IR (CCl_4) 2966, 2169, 1788, 1698, 145, 1343, 1193, 1120, 811 cm^{-1}; ^{1}H NMR δ 0.10 (s, 9H), 0.92 (d, J = 6.56 Hz, 3H), 1.12 (d, J = 6.84 Hz, 3H), 1.37 (d, J = 6.12 Hz, 3H), 2.90 (dd, J = 3.08 Hz, J = 10.28 Hz, 1H), 3.77 (m, 1H), 4.38 (m, 1H), 4.50 (d, 1H), 4.70 (d, 1H), 4.83 (m, 1H), 5.67 (d, J = 7.44 Hz, 1H), 7.38 (m, 10H). Anal. Calcd for $C_{28}H_{35}O_4Si$: C, 70.41; H, 7.39; N, 2.93. Found: C, 70.12; H, 7.39; N, 2.92.

Acetylenic Acid 62b. This material was prepared in 90% yield from 2.0 g (5.7 mmol) of Nicholas adduct **61b** in 75 mL of 3:1 THF/H_2O, 34 mL (17.0 mmol) of 0.50 M LiOH, and 5.1 mL (45.3 mmol) of 30% H_2O_2 by following the general procedure described above for acid **54a**. Chromatography (silica gel, 7:3:1 hexanes/EtOAc/HOAc) afforded 868 mg (90%) of **62b** as a glassy gum: R_f 0.64 (7:3:1 hexanes/EtOAc/HOAc); $[\alpha]^{25}_D$ = −14.62° (*c* 41.03, MeOH); IR (film) 3292, 2938, 2828, 2626, 2117, 1713, 1668, 1462, 1378, 1291, 1253, 1189, 1145, 1086, 977, 846, 800, 641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (2d, J = 7.2 Hz, 6H), 2.2 (s, 1H), 2.65 (m, 1H), 2.85 (m, 1H), 3.38 (s, 3H), 3.52 (dq, J = 3.48 Hz, 5.92 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 180.59, 81.40, 75.04, 72.24, 56.63, 41.69, 41.02, 16.83, 15.37; MS (EIMS) *m*/*z* 170 (M$^{+\bullet}$), 159, 129, 103, 85, 77, 69, 60; HRMS calcd for $C_9H_{14}O_3$ 170.1029, found 170.1022; HRMS calcd for ($C_9H_{14}O_3$ + H) 171.1029, found 171.1022. Also recovered was 800 mg (99%) of chiral auxiliary.

Acetylenic Acid 62c. This material was prepared in 90% yield from 2.99 g (6.97 mmol) of Nicholas adduct **61c** in 91 mL of 3:1 THF/H_2O, 42 mL (20.9 mmol) of 0.50 M LiOH, and 6.3 mL (55.8 mmol) of 30% H_2O_2 by following the general procedure described above for acid **54a**. Chromatography (silica gel, 7:2:1 hexanes/EtOAc/HOAc) afforded 1.54 g (90%) of **62c** as a glassy gum. Crystallization from hexane gave 1.39 g (81%) of **62c** as colorless prisms: mp 62−3 °C; R_f 0.7 (silica gel, 7:2:1 hexanes/EtOAc/HOAc); $[\alpha]^{25}_D$ = −30.72° (*c* 8.01, MeOH), IR (KBr) 3607,3492, 2990, 2937, 2882, 2255, 1755, 1453, 1324, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 7.02 Hz, 3H), 1.38 (d, J = 6.14 Hz, 3H), 2.22 (d, J = 2.55 Hz, 1H), 2.66 (m, 1H), 2.85 (m, 1H), 3.73 (m, 1H), 4.42 (d, J = 10.92 Hz, 1H), 4.70 (d, J = 10.92 Hz, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 180.10, 137.92, 128.29, 127.86, 127.64, 81.67, 72.32, 72.17, 70.50, 41.58, 41.15, 17.41, 15.35; MS (EIMS) *m*/*z* 246 (M$^+$), 202, 159, 140, 135, 111, 105, 97, 91, 54, 50, 42. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.31. Structure was confirmed by X-ray analysis.[22] Also recovered was 890 mg (98%) of chiral auxiliary.

Acetylenic Acid *ent*-62c. This material was prepared in 88% yield from 1.82 g (4.49 mmol) of Nicholas adduct *ent*-**61c** in 90 mL of 3:1 THF/H_2O, 27 mL (13.5 mmol) of 0.50 M LiOH, and 4.1 mL (35.9 mmol) of 30% H_2O_2 following the general procedure described above for acid **54a**. Chromatography (silica gel, 7:2:1 hexanes/EtOAc/HOAc) afforded 983 mg (88%) of *ent*-**62c** as a glassy gum, which upon crystallization from hexane had mp 62−3 °C, as well as identical spectral data as that from **62c** above. $[\alpha]^{25}_D$ = 30.82° (*c* 11.5, MeOH). Also recovered was 790 mg (99%) of chiral auxiliary.

Hydrazide 55b. This material was prepared in a fashion identical to that for hydrazide **20a** described above, using 167 mg (0.98 mmol) of acetylenic acid **62b**, 194 mg (1.0 mmol) of *N*-aminopyrrole **18b** in 25 mL of anhydrous THF, and 394 mg (2.1 mmol) of EDCI, which was stirred for 72 h at rt. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) gave 300 mg (88%) of **55b** as a white microcrystalline solid, mp 129−30 °C (EtOAc/hexanes); R_f 0.33 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = −13.17° (*c* 18, MeOH), IR (CH_2Cl_2) 3403, 3302, 2988, 2858, 1697, 1507, 1447, 1399, 1377, 1325, 1188, 1145, 1095, 961, 650, 586 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 7.0 Hz, 3H), 1.34 (d, J = 7.0 Hz, 3H), 1.73 (m, 4H), 2.26 (d, J = 2.44 Hz, 1H), 2.51 (m, 2H), 2.73 (m, 1H), 2.77 (m, 3H), 3.39 (s, 3H), 3.56 (m, 1H), 3.79 (s, 3H), 6.78 (s, 1H), 9.05 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 173.95, 161.64, 128.95, 125.09, 118.49, 115.87, 81.76, 74.49, 72.83, 56.76, 50.83, 41.51, 41.36, 23.66, 23.12, 23.08, 21.54, 16.98, 15.31. Anal. Calcd for $C_{19}H_{26}O_4N_2$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.80; H, 7.58; N, 8.06.

Hydrazide 55c. This material was prepared in a fashion identical to that for hydrazide **20a** described above, using 2.28 g (9.28 mmol) of acetylenic acid **62c**, 1.8 g (9.28 mmol) of *N*-aminopyrrole **18b** in 50 mL of anhydrous THF, and 2.39 g (12.4 mmol) of EDCI, which was stirred for 72 h at rt. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) gave 3.42 g (87%) of **55c** as a white microcrystalline solid: mp 99−100 °C (EtOAc/pentane); R_f 0.66 (40% EtOAc/hexanes); $[\alpha]^{25}_D$ = −21.06° (*c* 16, MeOH), IR (CH_2Cl_2) 3422, 2944, 1700, 1650, 1444, 1394, 1377, 1244, 1146, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 6.4 Hz, 3H), 1.39 (d, J = 6.0 Hz, 3H), 1.72 (m, 4H), 2.26 (d, J = 2.4 Hz, 1H), 2.50 (m, 2H), 2.77 (m, 4H), 3.75 (m, 1H), 3.78 (s, 3H), 4.46 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 6.68 (s, 1H), 7.38 (m, 5H), 8.99 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 174.08, 161.55, 137.94, 128.93, 128.30 (2), 127.97 (2), 127.67, 125.25, 118.37, 115.92, 82.01, 72.69, 71.56, 70.37, 50.78, 44.67, 41.53, 40.88, 23.60, 23.03,

22.98, 17.40, 15.08. Anal. Calcd for $C_{25}H_{30}O_4N_2$: C, 71.07; H, 7.16; N, 6.63. Found: C, 71.01; H, 7.19; N, 6.63.

Hydrazide 55d. This material was prepared in a fashion identical to that for hydrazide **20a** described above, using 147 mg (1.50 mmol) of 4-pentynoic acid, 290 mg (1.50 mmol) of *N*-aminopyrrole **18b** in 20 mL of anhydrous THF, and 860 mg (4.50 mmol, 3.0 equiv) of EDCI, which was stirred for 72 h at rt. Purification by flash chromatography (silica gel, 15% EtOAc/hexanes) gave 409 mg (96%) of **55d** as a white microcrystalline solid: mp 154−5 °C (EtOAc/hexanes); R_f 0.53 (40% EtOAc/hexanes); IR (KBr) 3261, 2936, 1699, 1531, 1445, 1267, 1248, 1097, 792, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.04 (d, 1H), 2.51 (m, 3H), 2.62 (m, 3H), 2.77 (m, 2H), 3.78 (s, 3H), 6.74 (s, 1H), 8.80 (br s, 1H); MS (EIMS) *m*/*z* 274 (M^+). Anal. Calcd for $C_{15}H_{18}O_3N_2$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.78; H, 6.65; N, 10.25.

***N*-Pyrrolo Enamide 56b.** This material was prepared in a fashion identical to that for *N*-pyrrolo enamide **56a** described above (method B), using 70.0 mg (0.20 mmol) of hydrazide **55b** in 7.0 mL of THF and 1.21 mL (1.21 mmol) of 1.0 M TBAF in THF. After the mixture was heated at reflux for 1 h, workup and purification by preparative TLC (silica gel, 250 μm, 30% EtOAc/hexanes) gave 49 mg (70%) of **56b** as a colorless gum: R_f 0.53 (30% EtOAc/hexanes); $[\alpha]^{25}_D = -11.92°$ (*c* 16, MeOH); ^{1}H NMR ($CDCl_3$) δ (two atropisomers) 1.20, 1.27. 1.40, 1.45 (4d, J = 6.4 HZ, 6H), 1.75 (m, 4H), 2.50 (m, 2H), 2.70 (m, 1H), 2.80 (m, 2H), 3.00 (m, 1H), 3.41, 3.73, 3.76 (3s, 6H), 3.60 (m, 1H), 3.85, 3.93, 4.20, 4.25 (4dd, J = 1 Hz, 2H), 6.51, 6.55 (2s, 1H). Anal. Calcd for $C_{19}H_{26}O_4N_2$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.85; H, 7.60; N, 8.09.

***N*-Pyrrolo Enamide 56c.** This material was prepared in a fashion identical to that for *N*-pyrrolo enamide **56a** described above (method B), using 194 mg (0.45 mmol) of hydrazide **55c** in 50 mL of THF, and 2.75 mL (2.75 mmol) of 1.0 M TBAF in THF. After the mixture was heated reflux for 2 h, workup and purification by preparative TLC (silica gel, 500 μm, 30% EtOAc/hexanes) gave 148 mg (76%) of **56c** as a colorless gum: R_f 0.77 (40% EtOAc/hexanes); $[\alpha]^{25}_D = -18.20°$ (*c* 15, MeOH); ^{1}H NMR ($CDCl_3$) δ (two atropisomers) 1.26 (d, J = 6.2 Hz, 3H), 1.45 (d, J = 7.6 Hz, 3H), 1.73 (m, 4H), 2.51 (m, 2H), 2.75−3.00 (m, 4H), 3.76 (s, 3H), 3.80 (m, 1H), 3.92 (t, J = 1.2 Hz, 1H), 4.17 (t, J = 1.2 Hz, 1H), 4.52 (d, 1H), 4.60 (d, 1H), 6.40 (s, 1H), 7.33 (m, 5H). Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.01; H, 7.19; N, 6.63. Found: C, 70.83; H, 7.16; N, 6.57.

***N*-Pyrrolo Enamide 56d.** This material was prepared in a fashion identical to that for *N*-pyrrolo enamide **56a** described above (method B), using 125 mg (0.46 mmol) of hydrazide **55c** in 15 mL of THF and 2.73 mL (2.73 mmol) of 1.0 M TBAF in THF. After the mixture was heated at reflux for 1 h, workup and purification by preparative TLC (silica gel, 1000 μm, 40% EtOAc/hexanes) gave 110 mg (88%) of **56d** as a colorless gum, which crystallized from EtOAc/hexane as a colorless solid: mp 167−68 °C; R_f 0.40 (40% EtOAc/hexanes); IR (CH_2Cl_2) 2940, 2858, 2253, 1745, 1697, 1575, 1605, 1455, 1402, 1308, 1241, 1189, 1102, 958, 911, 829, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.52 (m, 2H), 2.60−2.95 (m, 6H), 3.74 (s, 3H), 3.83 (d, J = 1.8 Hz, 1H), 4.15 (d, J =1.8 Hz, 1H), 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 173.17, 159.99, 145.55, 130.10, 123.26, 119.97, 115.32, 84.47, 50.79, 27.33, 23.76, 22.90, 22.80, 21.94, 21.49; MS (EIMS) *m*/*z* 274 ($M^{+\bullet}$). Anal. Calcd for $C_{15}H_{18}O_3N_2$: C, 65.68; H, 6.61; N,10.21. Found: C, 65.54; H, 6.61; N, 10.12. This compound was also prepared in 71% yield by following method A (*vide supra*).

Photolysis of *N*-Pyrrolo Enamide 56a (→ 29c, 32b, *E*-63a, *Z*-63a). Photolysis of 251 mg (0.83 mmol) of *N*-pyrrolo enamide **56a** for 16 h at −10 °C (300 nm, piperylene), by following the general procedure described above, afforded 98 mg (39%) of **63a** as a 47:51 *E*/*Z* mixture, 18 mg (7%) of recovered **56a**, 41 mg (16%) of pyrrole **32b**, and 32 mg (13%) of 1,5-isomer **29c** (not shown; *cf.* Scheme 5). Purification was accomplished by preparative TLC (silica gel).

***E*-63a**: yellow foam; R_f 0.2 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 38.04° (*c* 3.13, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 7.2 Hz, 3H), 1.28 (d, J = 7.3 Hz, 3H), 1.71 (m, 4H), 2.28 (dq, J = 3.2 Hz, 1H), 2.38 (m, 2H), 2.75 (m, 2H), 2.89 (m, 1H), 3.80 (s, 3H), 5.67 (s, 1H), 8.61 (br s, 1H), 8.91 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 179.57, 161.10, 143.40, 129.00, 128.06, 121.06, 116.83, 92.97, 51.08, 45.57, 40.25, 23.28, 23.12 (2), 21.68, 19.11, 17.02; MS (EIMS) *m*/*z* 302 (M^+), 270, 255, 242, 227, 111, 91, 78, 63; HRMS calcd for $C_{17}H_{22}O_3N_2$ 302.1630, found: 302.1627.

***Z*-63a**: colorless solid, mp 268−69 °C; R_f 0.38 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 40.18° (*c* 5.5, MeOH); IR (CH_2Cl_2) 3435, 1727, 1680, 1551, 1409, 1299, 1150, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 7.3 Hz, 3H), 1.34 (d, J = 6.9 Hz, 3H), 1.74 (m, 4H), 2.28 (dq, J = 7.3 Hz, 1H), 2.40 (m, 2H), 2.77 (dq, 1H), 2.79 (m, 2H), 3.82 (s, 3H), 5.27 (d, J = 1.92 Hz, 1H), 8.14 (br s, 1H), 8.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 180.06, 161.99, 141.93, 129.67, 128.16, 120.49, 117.23, 90.22, 50.98, 43.75, 42.28, 23.27, 23.24, 23.16, 21.95, 17.68, 14.77; MS (CIMS) *m*/*z* 303 (M + 1)$^+$; HRMS calcd for $C_{17}H_{22}O_3N_2$ 302.1630, found 302.1627. These data are identical to those of an authentic sample (following paper).

29c: colorless gum (solidifies in freezer); R_f 0.48 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = 37.01° (*c* 5.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.30 (2d, 6H, Me), 1.72 (m, 4H), 2.26 (m, 2H), 2.29 (m, 1H), 2.59 (m, 1H), 2.78 (m, 2H), 3.81 (s, 3H), 4.15 (d, J = 1.8 Hz, 1H), 4.24 (d, J = 1.8 Hz, 1H), 8.08 (br s, 1H).

Photolysis of *N*-Pyrrolo Enamide *ent*-56a (→ *ent*-29c, 32b, *ent*-*E*-63a, *ent*-*Z*-63a). Photolysis of 277 mg (0.92 mmol) of *N*-pyrrolo enamide *ent*-**56a** for 16 h at −10 °C (300 nm, piperylene), by following the general procedure described above, afforded 127 mg (46%) of *ent*-**63a** as a 55:72 *E*/*Z* mixture, 26 mg (9%) of recovered *ent*-**56a**, 26 mg (9%) of pyrrole **32b**, and 36 mg (13%) of 1,5-isomer *ent*-**29c** (not shown; *cf.* Scheme 5). Purification was accomplished by preparative TLC. Except for specific rotations, these materials were identical to the enantiomers derived from **56a** above. Specific rotations: *ent*-**29c**, $[\alpha]^{25}_D = -36.66°$ (*c* 2.7, MeOH); *ent*-*E*-**63a**, $[\alpha]^{25}_D = -38.08°$ (*c* 2.7, MeOH); *ent*-*Z*-**63a**, $[\alpha]^{25}_D = -40.98°$ (*c* 4.88, MeOH).

Photolysis of *N*-Pyrrolo Enamide 56b (→ 29d, 32b, *E*-63b, *Z*-63b). Photolysis of 41.2 mg (0.12 mmol) of *N*-pyrrolo enamide **56b** for 17 h at −10 °C (300 nm, piperylene), by following the general procedure described above, afforded 15.4 mg (37%) of **63b** as a 1:1 *E*/*Z* mixture, 8 mg (20%) of recovered **56b**, 4 mg (10%) of pyrrole **32b**, and 8 mg (20%) of 1,5-isomer **29d** (not shown; *cf.* Scheme 5). Purification was accomplished by preparative TLC (silica gel).

***Z*-63b**: pale yellow foam; R_f 0.30 (40% EtOAc/hexanes); $[\alpha]^{25}_D = -20.83°$ (*c* 8.21, MeOH); IR (CH_2Cl_2) 3437, 2931, 2821, 1732, 1686, 1591, 1497, 1455, 1366, 1298, 1238, 1189, 1083, 1018, 956, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 3H), 1.34 (d, J = 7.36 Hz, 3H), 1.75 (m, 4H), 2.41 (m, 2H), 2.62 (m, 1H), 2.78 (m, 2H), 2.98 (m, 1H), 3.39 (s, 3H), 3.58 (dq, 1H), 3.82 (s, 3H), 5.33 (d, J = 1.28 Hz, 1H), 8.26 (br s, 1H), 8.97 (br s, 1H); MS (EIMS) *m*/*z* 346 (M^+), 314, 270, 255, 244, 212, 170, 115, 84; (CIMS) 347 (M + 1)$^+$; HRMS calcd for $C_{19}H_{26}O_4N_2$ 346.1892, found 346.1880. Anal. Calcd for $C_{19}H_{26}O_4N_2$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.89; H, 7.60; N, 8.08.

***E*-63b**: yellow foam; R_f 0.15 (40% EtOAc/hexanes); $[\alpha]^{25}_D$ = −14.11° (*c* 5.1, MeOH); IR (CH_2Cl_2) 4314, 3260, 3060, 2988, 1723, 1662, 1391 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7.6 Hz, 3H), 1.28 (d, J = 7.6 Hz, 3H), 1.74 (m, 4H), 2.31 (m, 1H), 2.44 (m, 2H), 2.78 (m, 2H), 2.85 (m, 1H), 3.35 (m, 1H), 3.40 (s, 3H), 3.80 (s, 3H), 5.82 (s, 1H), 7.35 (br s, 1H), 10.61 (br s, 1H); MS (EIMS) *m*/*z* 346 (M^+), 314, 270, 255, 244, 212, 170, 115, 84; (CIMS) *m*/*z* 347 (M + 1)$^+$; HRMS calcd for $C_{19}H_{26}O_4N_2$ 346.1898, found 346.1894.

29d: pale yellow foam; R_f 0.42 (40% EtOAc/hexanes); $[\alpha]^{25}_D$ = −11.75° (*c* 9.7, MeOH); IR (CH_2Cl_2) 3431, 3061, 2974, 2937, 2859, 2826, 1727, 1690, 1593, 1509, 1382, 1330, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 3H), 1.34 (d, J = 7.3 Hz, 3H), 1.73 (m, 4H), 2.30 (m, 2H), 2.70 (m, 1H), 2.83 (m, 2H), 2.90 (m, 1H), 3.41 (s, 3H), 3.60 (dq, 1H), 3.84 (s, 3H), 4.28 (dt, J = 1.2 Hz, 2H), 8.72 (br s, 1H).

Photolysis of *N*-Pyrrolo Enamide 56d (→ 32b, *E*-63d, *Z*-63d). Photolysis of 150 mg (0.55 mmol) of *N*-pyrrolo enamide **56d** for 36 h at −10 °C (300 nm, piperylene), by following the general procedure described above (rigorous exclusion of air), afforded 90.3 mg (60%) of **63d** as a 1:1 *E*/*Z* mixture, 30 mg (20%) of recovered **56d**, and 12 mg (8%) of

pyrrole **32b**. Purification was accomplished by preparative TLC (silica gel).

***E*-63d**: pale yellow foam; R_f 0.24 (40% EtOAc/hexanes); IR (CH_2Cl_2) 3412, 3224, 2931, 2848, 2343, 1695, 1568, 1501, 1454, 1390, 1237, 1196, 1143, 1084, 1049, 1020, 796, 614, 514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.41 (m, 2H), 2.66 (m, 2H), 2.76 (br m, 2H), 3.05 (m, 2H), 3.82 (s, 3H), 5.68 (s, 1H), 8.22 (br s, 1H), 8.39 (br s, 1H); MS (CIMS) *m/z* 274 (M^+); HRMS calcd for $C_{15}H_{18}O_3N_2$ 274.1317, found 274.1323.

***Z*-63d**: colorless microcrystalline solid, mp 272−3 °C (ethyl acetate); R_f 0.37 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 1.73 (br m, 4H), 2.40 (br m, 2H), 2.58 (t, J = 7.1 Hz, 2H), 2.78 (br m, 2H), 2.91 (t, 2H), 3.80 (s, 3H), 5.28 (s, 1H), 8.46 (br s, 1H), 8.95 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 172.21, 160.39, 127.12, 125.34, 116.81, 114.13, 94.22, 72.15, 50.77, 34.27, 22.77, 22.59, 21.33, 15.35; MS (CIMS) *m/z* 274 (M^+); HRMS calcd for $C_{15}H_{18}O_3N_2$ 274.1317, found 274.1336. Anal. Calcd for $C_{15}H_{18}O_3N_2$: C, 65.88; H, 6.61; N, 10.21. Found: C, 64.75; H, 6.70; N, 10.17.

Hydrazide 65b. This material was prepared in a fashion identical to that for hydrazide **20a** described above, using 127 mg (0.75 mmol) of acetylenic acid **62b**, 254 mg (0.75 mmol) of *N*-aminopyrrole **64**[23] in 30 mL of anhydrous THF, and 430 mg (2.24 mmol, 3.0 equiv) of EDCI, which was stirred for 40 h at rt. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) gave 279 mg (88%) of **65b** as a white microcrystalline solid: mp 96−8 °C (EtOAc/hexanes); R_f 0.60 (40% EtOAc/hexanes); $[\alpha]^{25}_D$ = −20.69° (*c* 16.8, MeOH), IR (CH_2Cl_2) 3409, 3306, 2982, 2936, 1722, 1453, 1425, 1376, 1141, 1089, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.2 Hz, 3H), 1.31 (d, J = 6 Hz, 3H), 1.32 (t, 3H), 1.99 (s, 3H), 2.24 (d, 1H), 2.49 (m, 2H), 2.69 (m, 1H), 2.78 (m, 1H), 2.98 (m, 2H), 3.36 (s, 3H), 3.53 (m, 1H), 3.68 (s, 3H), 4.25 (q, 2H) 6.77 (s, 1H), 9.18 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 173.84, 173.52, 160.85, 129.26, 126.56, 117.53, 116.47, 81.72, 74.40, 72.78, 60.02, 56.68, 51.49, 41.44, 41.19, 34.77, 21.18, 16.92, 15.22, 14.20, 9.60; MS (CIMS) *m/z* 407 (M + 1)$^+$; (EIMS) *m/z* 406 (M^+), 254, 239, 181, 166, 135, 125, 93, 77, 65; HRMS calcd for $C_{21}H_{30}O_6N_2$: 406.2103. Found: 406.2113.

***N*-Pyrrolo Enamide 66b.** This material was prepared in a fashion identicl to that for *N*-pyrrolo enamide **56a** described above (method B), using 200 mg (0.47 mmol) of hydrazide **65b** in 20 mL of THF, and 2.82 mL (2.82 mmol) of 1.0 M TBAF in THF. After the mixture was heated at reflux for 30 min, workup and purification by preparative TLC (silica gel, 500 μm, 30% EtOAc/hexanes) gave 140 mg (70%) of **56d** as a colorless gum: R_f 0.66 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ = −14.69° (*c* 4.69, MeOH); IR (CH_2Cl_2) 3020, 2984, 2934, 2825, 2400, 1737, 1696, 1655, 1502, 1450, 1385, 1211, 1141, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ (two rotomers) 1.20−1.45 (4d, 2t, 9H), 2.03 (s, 3H), 2.56 (m, 2H), 2.66 (m, 1H), 3.00 (m, 1H), 3.05 (m, 2H), 3.43 (s, 3H), 3.60 (m, 1H), 3.68 (s, 3H), 3.78−3.83 (2s, 1H), 4.20−4.30 (2s + 1dq, 3H), 6.55−6.60 (2s, 1H); ^{13}C NMR ($CDCl_3$) δ 174.33, 172.92, 159.23, 147.58 (147.19), 130.64 (128.27), 128.02 (127.78), 125.45 (125.31), 118.08 (118.05), 84.50 (83.89), 78.51 (78.05), 59.94 (59.89), 56.23 (56.08), 51.04, 47.56, (46.94), 35.63 (35.50), 35.03, 21.88, 17.37 (17.12), 15.19 (14.51), 14.12 (14.08), 9.65.

Photolysis of *N*-Pyrrolo Enamide 66b (→ 29e, 32c, *E*-67b, *Z*-67b). Photolysis of 140 mg (0.35 mmol) of *N*-pyrrolo enamide **66b** for 20 h at −10 °C (300 nm, piperylene), by following the general procedure described above, afforded 64.7 mg (46%) of **67b** as a 34:31 *E*/*Z* mixture, 32.7 mg (23%) of recovered **66b**, 17.9 mg (13%) of pyrrole **32c** (not shown; *cf.* Scheme 5), and 21.2 mg (15%) of 1,5-isomer **29e** (not shown; *cf.* Scheme 5). Purification was accomplished by preparative TLC (silica gel).

***E*-67b**: yellow foam; R_f 0.28 (50% EtOAc/hexanes); $[\alpha]^{25}_D$ = −8.9° (*c* 9.1, MeOH); IR (CH_2Cl_2) 3415, 3256, 2934, 2875, 2360, 1727, 1695, 1560, 1503, 1456, 1382, 1166, 1137, 1112, 1057, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 7.2 Hz, 3H),1.36 (d + t, J = 7.2 Hz, 6H), 1.99 (s, 3H), 2.31 (m, 1H), 2.57 (m, 2H), 2.82 (m, 1H), 3.05 (m, 2H), 3.37 (m, 1H), 3.43 (s, 3H), 3.69 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 5.92 (s, 1H), 7.58 (br s, 1H), 10.85 (br s, 1H); MS (EIMS) *m/z* 406 (M^+) 202, 178, 149, 124, 95, 84, 69; (CIMS) *m/z* 407 (M + 1)$^+$; HRMS calcd for $C_{21}H_{30}O_6N_2$ 406.2100, found 406.2131.

***Z*-67b**: pale yellow foam; R_f 0.42 (50% EtOAc/hexanes); $[\alpha]^{25}_D$ = −7.75° (*c* 8.9, MeOH); IR (CH_2Cl_2) 3430, 3276, 2933, 2878, 2826, 2254, 1731, 1681, 1570, 1501, 1456, 1377, 1300, 1172, 1136, 1097, 1056, 961 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.2 Hz, 3H), 1.32 (d, J = 7.4 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.97 (s, 3H), 2.54 (m, 2H), 2.60 (m, 1H), 2.96 (m, 1H), 3.09 (m, 2H), 3.40 (s, 3H), 3.60 (m, 1H), 3.69 (s, 3H), 4.29 (q, J = 7.2 Hz, 2H), 5.35 (s, 1H), 7.99 (br s, 1H), 8.89 (br s, 1H); MS (EIMS) *m/z* 406 (M^+), 202, 179, 149, 124, 111, 95, 84, 69; (CIMS) *m/z* 407 (M + 1)$^+$; HRMS calcd for $C_{21}H_{30}O_6N_2$ 406.2100, found 406.2079.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **53**−**56** and **61**−**67** (29 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.

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