Dihydropyrromethenones by Pd(0)-Mediated Coupling of Iodopyrroles and Acetylenic Amides. Synthesis of the A,B-Ring Segment of Phytochrome

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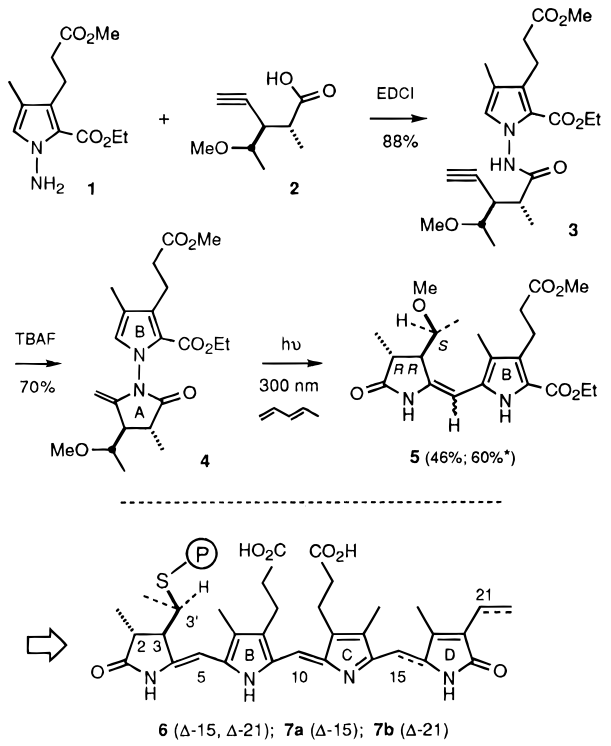
Received February 14, 1997[⊗]

Dihydropyrromethenone derivative **32b**, which constitutes the A,B-ring segment of phytochrome (**6**), has been prepared in enantiomerically pure form beginning with acetylenic amide **47b** and iodopyrrole **27**. The key steps involved the TBAF-catalyzed 5-*exo-dig* cyclization of the acetylenic pyrrole **48b**, followed by thia-Mitsunobu inversion of the resulting alcohol derivative **31b**.

Introduction

In the accompanying paper of this series we described a novel synthesis of dihydropyrromethenone **5**,[1a] a potential synthetic precursor to the biologically important plant pigment phytochrome (**6**) and related materials (Scheme 1). Phytochrome is a biliprotein that plays a

Scheme 1



key role in photomorphogenesis, the process by which light governs the growth, development, and aging of plants.[1a,2] The same A,B-ring segment (**5**) is also found in light-harvesting pigments such as phycocyanin (**7a**) and phycoerythrin (**7b**), which serve as auxiliary chromophores in photosynthesis.[3]

In comparison to photosynthesis, where some aspects of the mechanism are known in considerable detail, relatively little is known about photomorphogenesis at the molecular level. In part this is due to a lack of suitable model systems, as well as to the difficulty of isolating and purifying the parent chromophore (**6** is present in much lower concentrations in plants than chlorophyll). In order to address these issues we have begun a synthetic program that we hope will serve two purposes: (1) to provide ample quantities of material to study the fundamental photochemistry of **6** and (2) to prepare labeled phytochromobilin intermediates for reconstitution with recombinant apophytochrome. This last approach offers perhaps the best opportunity for studying *E,Z* isomerization in the protein-bound chromophore, a likely step in phytochrome activation.[1a,4] Ultimately this work might lead to a better understanding of the process of photomorphogenesis.

Our previous studies took advantage of the ready availability of *N*-aminopyrroles of type **1**[5] and acetylenic acids **2** (Scheme 1).[1a,6] These compounds contain all of the stereo- and regiochemical features necessary for eventual conversion to dihydropyrromethenone **5**. Thus, EDCI-mediated coupling of **1** and **2** afforded an excellent yield of the acetylenic hydrazide **3**, which upon F^--catalyzed 5-*exo-dig* cyclization gave *N*-pyrroloenamide **4** in enantiomerically pure form (TBAF = *n*-Bu_4NF). This last step completes the formation of ring A, and it is significant for the fact that hydrazide cyclization takes place with an unactivated alkyne (*vide infra*).[1] Finally, photochemical 3,5-sigmatropic rearrangement of **4** gave a 46% yield of the target compound **5** as a ∼1:1 mixture of *E* and *Z* isomers (60% yield based on recovered **4**). Also produced were varying amounts of products derived from 1,3- and 1,5-rearrangements.

The utility of this approach stems partly from the ease of preparation of its starting components,[1a,5] which allows

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

(1) (a) Jacobi, P. A.; Buddhu, S. C.; Fry, D.; Rajeswari, S., *J. Org. Chem.* **1997**, *62*, 2894. (b) Jacobi, P. A.; Buddhu, S. C. *Tetrahedron Lett.* **1988**, *29*, 4823. Preliminary communications: (c) Jacobi, P. A.; Rajeswari, S. *Tetrahedron Lett.* **1992**, *33*, 6235. (d) Jacobi, P. A.; Guo, J.; Zheng, W. *Tetrahedron Lett.* **1995**, *36*, 1197.

(2) *Phytochrome and Photoregulation in Plants*; Furuya, M. Ed.; Academic Press: New York, 1987. See also footnote 6 in ref 1a.

(3) Scheer, H. *Angew. Chem.* **1981**, *93*, 230; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 241. See also footnotes 8 and 9 in ref 1a.

(4) (a) Thümmler, F.; Rüdiger, W. *Tetrahedron* **1983**, *39*, 1943. (b) Rüdiger, W.; Thümmler, F.; Cmiel, E.; Schneider, S. *Proc. Natl. Acad. Sci., U.S.A.* **1983**, *80*, 6244. (c) Farrens, D. L.; Holt, R. E.; Rospendowski, B. N.; Song, P.-S.; Cotton, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 9162. (d) Fodor, S. P. A.; Lagarias, J. C.; Mathies, R. A. *Biochemistry* **1990**, *29*, 11141. (e) Fodor, S. P. A.; Lagarias, J. C.; Mathies, R. A. *Photochem. Photobiol.* **1988**, *48*, 129. (f) Cornejo, J.; Beale, S. I.; Terry, M. J.; Lagarias, J. C. *J. Biol. Chem.* **1992**, *267*, 14790. (g) Wahleithner, J. A.; Li, L.; Lagarias, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 10387. (h) Li, L.; Lagarias, J. C. *J. Biol. Chem.* **1992**, *267*, 19204

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

(6) (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.

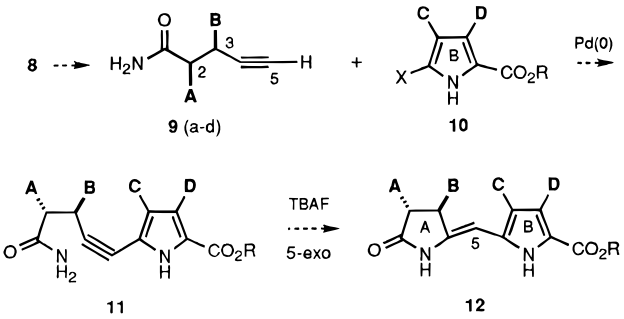
S0022-3263(97)00289-2 CCC: $14.00

for considerable flexibility in introducing substituents on the tetrapyrrole skeleton. However, a number of limitations remain. First, photochemical rearrangement of **4** to **5** invariably leads to ~1:1 mixtures of *E* and *Z* isomers at C_4-C_5, while the natural stereochemistry at this position is *Z*. Second, protecting groups must be chosen with care to avoid complications arising from triplet-sensitized hydrazide cleavage.[1a] Third, yields, although moderate to good (40−60%), have been optimized and there is probably little opportunity for improvement. In this paper we describe an alternative synthesis of dihydropyrromethenones of type **5** that remedies each of these deficiencies, while still retaining the most positive features of our original strategy. Also, we have prepared a viable precursor to phytochrome (**6**) that incorporates the natural substitution pattern.

Discussion and Results

The cyclization of hydrazide **3** to enamide **4** took advantage of the exceptional catalytic activity of TBAF,[7a] which was discovered in a serendipitous fashion upon attempted cleavage of certain (trimethylsilyl)acetylene derivatives with F^- (Scheme 9 in ref 1a).[1a] This discovery was of interest since it demonstrated that even unactivated alkynes could undergo ring-A cyclization (formerly this transformation was successful only with acetylenic esters[1b]). Consequently, we set out to explore a number of modifications to our original strategy that previously did not appear to be feasible. One such modification is outlined in Scheme 2. As with alkyne **2**, we expected that

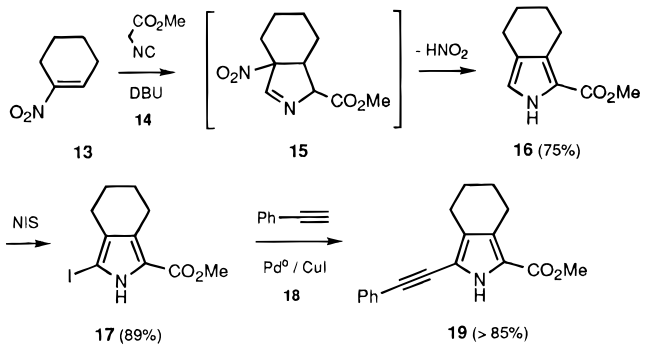
Scheme 2



ring-A synthons **9** could be prepared in enantiomerically pure form from the acetylenic acids **8**, themselves derived with unequivocal control over stereochemistry using a Nicholas−Scheiber reaction.[1a,6] However, in this case bond connectivity between C_5 and C_6 would be established *via* Pd(0)-mediated coupling of halopyrroles **10** with acetylenic amides **9**. Acetylenic pyrroles **11** would then be converted directly to dihydropyrromethenones **12** by TBAF-catalyzed 5-*exo*-*dig* cyclization, in close analogy to the cyclization of **3** to **4** (*cf.* Scheme 1). This sequence represents a significant improvement over that outlined in Scheme 1, since it eliminates the need for a subsequent 3,5-sigmatropic rearrangement. Finally, it seemed likely that kinetic control in the amide addition to the alkyne triple bond would lead directly to the naturally occurring *Z* configuration at C_4-C_5.

At the time we began this work, only scattered reports had appeared describing the coupling of acetylenes with halopyrroles,[9] and few provided experimental details. Therefore, our initial studies were carried out with the model iodopyrrole **17**, which was readily prepared by iodination of 2-carbomethoxy-3,4-butane-1,4-diylpyrrole (**16**), itself derived in 75% yield from 1-nitrocyclohexene (**13**) and methyl isocyanoacetate (**14**) using the methodology of Zard *et al.* (Scheme 3).[10] Iodopyrrole **17** afforded

Scheme 3



a 21% yield of pyrroloacetylene **19** upon coupling with phenylacetylene (**18**) using the reagent combination $PdCl_2(Ph_3P)_2$/CuI in NEt_3 as a solvent.[8] The major byproduct in this case was the bis(acetylene) PhC≡C-C≡CPh (**20**) arising from oxidative dimerization of **18**. Similar results were obtained using $Pd(PPh_3)_4$ and most other Pd(0) catalysts, although modest improvements were observed with $Pd[P(o\text{-tolyl})_3]_4$.[11] A number of variations in solvent (THF, MeCN, DMF) and molar ratio of **18:17** were also explored, all with the catalyst system $Pd(PPh_3)_4$/CuI/NEt_3. In general, DMF provided the cleanest reactions,[12] while ratios of **18:17** as high as 2:1 afforded slight increases in yields of coupling product **19**, together with much larger quantities of dimer **20**. However, by far the most important factor influencing yields in these reactions was the presence of oxygen. At least three freeze−thaw cycles are necessary for optimum yields of **19** and to minimize formation of **20**.[13] Thus, our best results were obtained with a ratio of **18:17** = 1.1:1.0, using DMF as the solvent under rigorously degassed conditions (*cf.* Experimental Section). This protocol appeared to be general for the Sonogashira coupling of 1*H*-2-iodopyrroles with acetylenes[8,9e] and consistently afforded **19** in >85% yield with little or no dimer formation.

(7) (a) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429. (b) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644. (c) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.

(8) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. For related methodology, see: (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (d) Stephans, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(9) (a) Vasilevskii, S. F.; Sundukova, T. A.; Shvartsberg, M. S.; Kotylarevskii, I. L. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1979**, 1536 (p 1661 in Russian); *cf. Chem. Abstr.* **1979**, *91*, 157544g. (b) Vasilevskii, S. F.; Sundukova, T. A.; Shvartsberg, M. S.; Kotylarevskii, I. L. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1980**, 1871; *cf. Chem. Abstr.* **1981**, *94*, 30464n. (c) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653. (d) Chen, W. Ph.D. Dissertation, Department of Chemistry, University of Alabama, Tuscaloosa, 1990. (e) Coupling appears to be much slower with 1-Boc-2-iodopyrroles.

(10) (a) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587. See also: (b) May, D. A.; Lash, T. D. *J. Org. Chem.* **1992**, *57*, 4820. (c) Baulder, C.; Ocampo, R.; Callot, H. J. *Tetrahedron* **1992**, *48*, 5135. (d) Tang, J.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793. (e) Jacobi, P. A.; DeSimone, R. W. *Tetrahedron Lett.* **1992**, *33*, 6231.

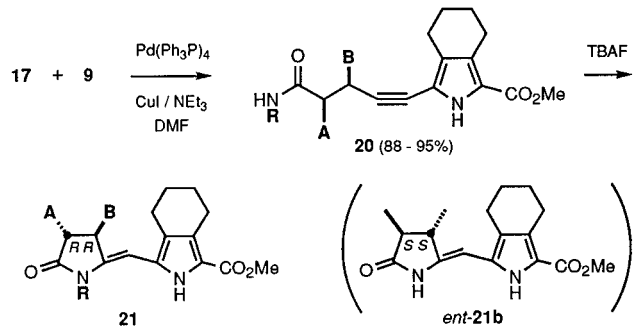
(11) (a) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(12) Robins, M. J.; Vinayak, R. S.; Wood, S. G. *Tetrahedron Lett.* **1990**, *31*, 3731.

(13) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.

These experiments were readily extrapolated for use with more complicated acetylenic amides of type **9** (Scheme 4). In every case, Pd(0)-mediated coupling of

Scheme 4



(a): A, B, C = H. (b): A, B = Me; R = H. (c): A = Me; B = *S*-CHOMeCH$_3$; R = H. (d): A = Me; B = *S*-CHOBnCH$_3$; R = H. (e): A, B = H; R = Bn.

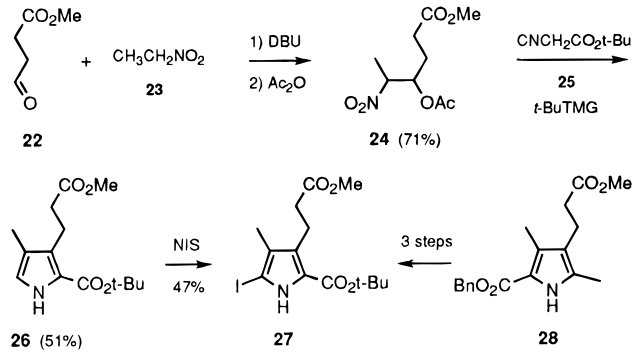
Cmpd	A	B	R	Yield	$[\alpha]^{25}_D$ (*Z*)
21a	H	H	H	25%	0.00°
21b	Me	Me	H	83%	+41.52°
21c	Me	*S*-CHOMeCH$_3$	H	78%	-20.46°
21d	Me	*S*-CHOBnCH$_3$	H	75%	+8.14°
ent-**21b**	Me	Me	H	81%	-41.00°
21e	H	H	Bn	73%	0.00°

iodopyrrole **17** with acetylenic amides **9a**−**e** and *ent*-**9b** was accomplished in yields of >88%. Significantly, there was no need to protect either the amide or pyrrole components. Furthermore, cyclization of pyrroloacetylenes **20a**−**e** and *ent*-**20b** occurred under conditions nearly identical to those employed in the conversion of acetylenic hydrazide **3** to cyclic enamide **4** (TBAF, THF, reflux), affording *Z* dihydropyrromethenones **21b**−**e** and *ent*-**21b** in 73−83% yield. Little or no formation of the corresponding *E* isomers was observed, except for the case of **21e** (R = Bn), where steric crowding causes partial *Z*,*E* isomerization. The materials thus obtained were identical to, in both physical properties and optical rotation, the corresponding *Z* isomers prepared using our photochemical strategy.[1a]

Several characteristics of this cyclization warrant special mention. First, for maximum yield it is essential that cyclization be carried out under strictly anaerobic conditions (≥ three freeze−thaw cycles). Second, cyclization occurs faster with more highly substituted substrates (rate: A, B = Me, *S*-CHORCH$_3$ ≈ Me, Me > H, H; also **21e** [R = Bn] > **21a** [R = H]) and is very slow with simple aliphatic acetylenic amides lacking a conjugated pyrrole ring. Finally, all of these cyclizations exhibit a brief induction period prior to the onset of reaction. This last characteristic might indicate that the actual catalytic species is the thermodynamically stable *n*-Bu$_4$N$^+$FHF$^-$ complex ("tetra-*n*-butylammonium bifluoride").[14] This material forms rapidly upon heating *n*-Bu$_4$NF in solution and upon attempted drying of *n*-Bu$_4$NF·3H$_2$O at 40−70 °C.[14a] Indeed, it is likely that *n*-Bu$_4$N$^+$FHF$^-$ is also involved in other F$^-$-catalyzed reactions which specify the use of TBAF at *T* > 40 °C.[14b,c]

Before extending these studies to the synthesis of dihydropyrromethenones of type **5**, it was necessary to devise an efficient preparation of the iodopyrrole **27**. This

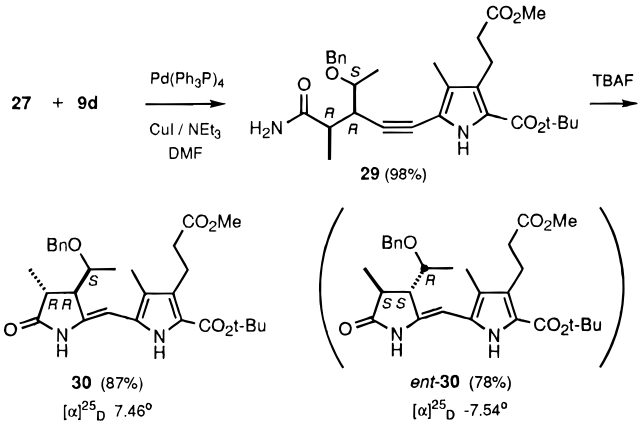
Scheme 5



was accomplished using either of the routes outlined in Scheme 5. The first of these makes use of the methodology of Zard *et al.*,[10] which we had previously employed in the synthesis of pyrrole **16** (*cf.* Scheme 3). In this case, aldehyde **22** was first converted to the Henry adduct **24** by DBU-catalyzed condensation with nitroethane (**23**), followed by acylation with acetic anhydride. In the presence of base, **24** underwent rapid elimination of HOAc, followed by Michael addition with *tert*-butyl isocyanoacetate (**25**) and ring closure to afford the desired pyrrole **26** in a single step.[10e] A wide range of base/solvent combinations was explored in order to optimize the transformation of **24** to **26**. However, we eventually found that the system *tert*-butyltetramethylguanidine/isopropyl alcohol consistently gave the best yields.[10] Iodination of **26** with NIS then gave a 47% yield of the ring-C precursor **27** on a 0.5−1 g scale. As an alternative route to **27**, Rapoport *et al.* have recently described an efficient procedure for the oxidative degradation of benzyl ester **28**, which ultimately affords **27** by decarboxylative iodination.[15a] Although this sequence is somewhat longer, it works quite well for preparing **27** on multigram scales (>5 g).

Iodopyrrole **27** proved to be an excellent precursor for dihydropyrromethenones related to tetrapyrroles **6**−**7b** (Scheme 6). Thus, in a very efficient two-step sequence,

Scheme 6



Pd(0)-catalyzed coupling of **27** with the enantiomerically pure amide **9d** gave a virtually quantitative yield of the acetylenic pyrrole **29**, which upon TBAF-induced cyclization as described above afforded the ring-A,B precursor **30** in 87% yield. In identical fashion, but beginning with

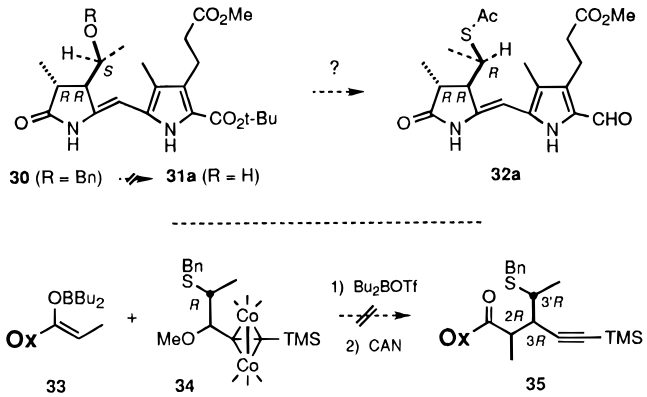
(14) (a) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112. (b) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644. (c) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

(15) (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. See also: (b) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1971**, 502. (c) Sessler, J. L.; Mozaffari, A.; Johnson, M. R. *Org. Synth.* **1991**, *70*, 68.

acetylenic amide *ent*-**9d**, enantiomer *ent*-**30** was also prepared as a single isomer, and with $[\alpha]^{25}_D$ of essentially equal magnitude but opposite sign. The results summarized in Schemes 4 and 6 are considerably better than those obtained by following our original strategy (Scheme 1),[1a] and we believe that this methodology has significant advantages over traditional approaches.

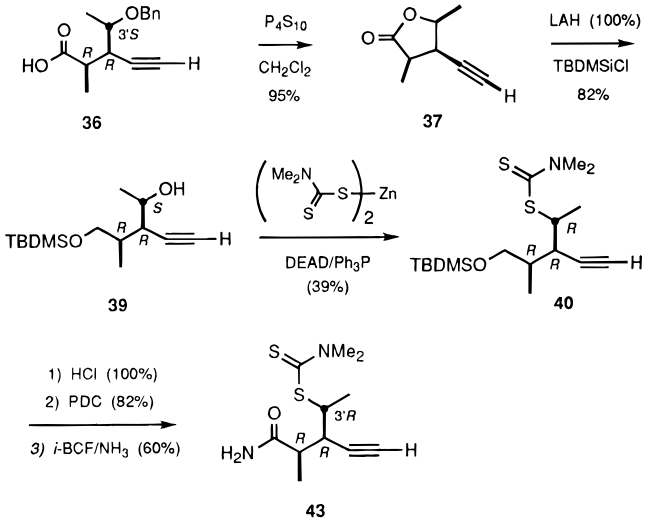
We initially planned that (3′*R*)-dihydropyrromethenone **32a** might be derived *via* thia-Mitsunobu inversion of 3′-(*S*)-hydroxy derivative **31a** (R = H),[1a,16] followed by decarboxylative formylation (Scheme 7).[17] This transformation would give material having the 2*R*,3*R*,3′*R* configuration found in tetrapyrroles **6**−**7b**, in suitable form for coupling with an appropriate C,D-ring fragment.[17] However, this approach failed, since **30** (R = Bn) suffered extensive decomposition upon attempted benzyl ether cleavage to afford **31a**. Reagents tested included H_2/Pd, BBr_3, Me_3SiI, and P_4S_{10} (*vide infra*). We also explored the possibility that 3′*R* mercaptide derivatives of type **35** might be prepared directly using the Nicholas−Schreiber methodology (Scheme 7).[6] Surprisingly, however, all attempts at condensing boron enolates of type **33** with the cobalt complex **34** were unsuccessful. At low temperatures little or no reaction occurred, while more forcing conditions caused rapid decomposition. This failure is most likely due to mercaptide complexation with Bu_2BOTf, which inhibits the requisite homolytic cleavage in **34** to generate carbocation intermediates.[6a] In any event, as described elsewhere,[18] mismatched condensations of this type typically proceed with *anti* selectivity.

Scheme 7

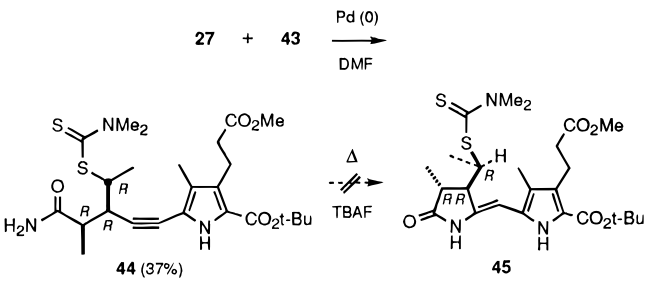


These difficulties were partly circumvented with the experiments outlined in Scheme 8. Thus, debenzylation of acetylenic acid **36** with P_4S_{10} led directly to the lactone derivative **37** (95%),[1a,19] which upon LAH reduction and selective protection (TBDMSiCl) gave an 82% yield of the secondary alcohol **39**. This last material then underwent thia-Mitsunobu inversion with the reagent system ZIRAM/DEAD/Ph_3P,[20] affording a 39% yield of the desired 2*R*,3*R*,3′*R* mercaptide **40**. Once in hand, **40** was converted in 49% overall yield to the acetylenic amide **43** by a three-step sequence involving deprotection, oxidation, and finally amidation with isobutyl chloroformate (*i*-BCF) and NH_3. Although circuitous, this route was suitable for preparing gram quantities of **43** with excellent stereocontrol. At this stage, however, we were disappointed to find that **43** gave only modest yields of the acetylenic pyrrole **44** upon Pd(0)-mediated coupling with the iodopyrrole **27** (Scheme 9). Presumably sulfur interferes in this case by poisoning the Pd catalyst. Even more discouraging, all attempts at effecting cyclization of **44** to the corresponding dihydropyrromethenone **45** gave only extensive decomposition.

Scheme 8



Scheme 9



On the basis of these results, we concluded that thia-Mitsunobu inversion at $C_{3'}$ could only be effected *after* formation of the dihydropyrromethenone ring. Until now, however, all attempts at cleaving protected hydroxyl derivatives of type **30** had failed (*cf.* Scheme 7). Fortunately, this problem was resolved with the finding that lactone **37** underwent facile ring opening with a variety of amines **46**, affording acetylenic alcohols of type **47** in 90−95% yield (Scheme 10). Alkynes **47a,b** (R = H, PMB) then gave 80−95% yields of the corresponding pyrroloacetylenes **48a,b** upon Pd(0)-catalyzed coupling with iodopyrrole **27**.

With ample quantities of both **48a** (R = H) and **48b** (R = Bn) now in hand, we turned our attention to the remaining steps necessary to complete the synthesis of **32** (Scheme 10). Unexpectedly, cyclization of **48a** turned out to be relatively slow, affording a 43% yield of **31a**

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

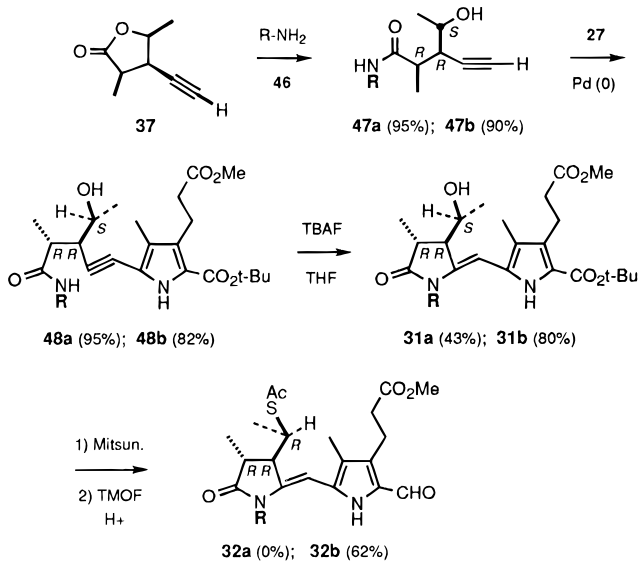
(17) (a) Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024. (b) Bishop, J. E.; Dagam, S. A.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1876. (c) Gossauer, A.; Hirsch, W. *Liebigs Ann. Chem.* **1974**, 1496. (d) Gossauer, A.; Hinze, R.-P. *J. Org. Chem.* **1978**, *43*, 283. (e) Gossauer, A.; Weller, J.-P. *Chem. Ber.* **1980**, *113*, 1603.

(18) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413.

(19) Cleavage of benzyl ethers with P_4S_{10} does not appear to be a general reaction, but this reagent works well with carboxylic acids where intramolecular participation is possible.

(20) (a) Rollin, P. *Tetrahedron Lett.* **1986**, *27*, 4169. (b) Rollin, P. *Synth. Commun.* **1986**, *16*, 611.

Scheme 10



(**a**): R = H; (**b**): R = *p*-methoxybenzyl (PMB)

after 48 h at reflux with 6 equiv of TBAF. In addition, all attempts at carrying out the required thia-Mitsunobu inversion with **31a** failed. This failure appears to be due to interference by the free lactam group in ring A, which underwent competitive reaction with DEAD. In any event, much more satisfactory results were obtained with **48b** (R = PMB), which gave an 80% yield of 3′(*S*)-hydroxydihydropyrromethenone **31b** upon brief warming with 1 equiv of TBAF (*Z* isomer exclusively). This result is in accord with our previous observations pertaining to the rate-enhancing effect of N-substitution on amide cyclizations (*cf.* also **21a** vs **21e** in Scheme 4).[21] Under identical conditions (6 equiv of TBAF/1 h or 1 equiv of TBAF/21 h), **48a** gave <10% of **31a**. Finally, we were pleased to find that **31b** gave a 62% overall yield of the desired ring-A,B precursor **32b** upon thia-Mitsunobu inversion,[16] followed by acid-catalyzed decarboxylative formylation.[17] We believe that **32b** represents a convenient ring-A,B synthon for eventual elaboration to phytochrome (**6**).

Summary

Synthetic studies in this area are important, since at present we have little understanding of how phytochrome (**6**) governs the growth, development, and aging of plants (photomorphogenesis). In part this is due to a lack of suitable model systems, as well as to the difficulty of isolating and purifying the parent chromophore. The methodology described in this paper is highly flexible, and it allows for excellent control over both relative and absolute stereochemistry, as well as regiochemistry along the backbone of the tetrapyrrole skeleton. Flexibility of this type is important not only for the synthesis of **6** but also for the preparation of specifically labeled phytochrome analogs.

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. Solvents and reagents were purified as described in the accompanying article.

4-Pentynoic Acid Amide (9a). A solution of 2.0 g (20.4 mmol) of 4-pentynoic acid (**8a**)[1a] in 20 mL of dry benzene was treated with 1.64 mL (22.4 mmol, 1.1 equiv) of $SOCl_2$, and the reaction mixture was stirred for 4 h at rt and then heated at reflux for 1 h. At the end of this period, the excess $SOCl_2$ and benzene were removed under reduced pressure, and the residue was taken up in 10 mL of anhydrous THF, cooled to −78 °C, and treated with 1.0 mL of dry NH_3 condensed from a cylinder. The reaction mixture was then allowed to come slowly to rt and was stirred for an additional 8 h. The THF was then removed under reduced pressure, and the residue was taken up in 10 mL of H_2O and extracted with 3 × 10 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue crystallized from EtOAc to afford 1.90 g (94%) of **9a** as a colorless crystalline solid: mp 112−3 °C; R_f 0.45 (50% acetone/hexanes); IR (KBr) 3379, 2235, 1663, 1424, 1136, 1078, 645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (d, J = 2.4 Hz, 1H), 2.45 (m, 2H), 2.55 (m, 2H), 5.65 (br s, 2H); MS (EIMS) m/z 97 ($M^{+\bullet}$). Anal. Calcd for C_5H_7NO: C, 61.84; H, 7.27; N,14.42. Found: C, 61.80; H, 7.29; N, 14.38.

General Procedure for the Preparation of Acetylenic Amides 9b−d and *ent*-9b,d. A solution of 1.5−10.0 mmol (1.0 equiv) of the appropriate carboxylic acid **8**[1a] in 15−50 mL of anhydrous THF was cooled to 0 °C under argon and was treated with vigorous stirring with 1.0 equiv of NEt_3, followed by 1.0 equiv of isobutyl chloroformate. A white precipitate of Et_3N·HCl formed immediately, and the reaction mixture was stirred at 0 °C for an additional 30 min to form the mixed anhydride. The resultant suspension was then filtered directly *via* cannula into an excess of dry liquid NH_3 (~1 mL, inverse addition) that had been cooled to −78 °C. After the addition was complete, the reaction mixture was allowed to come to rt over a period of 3 h and was then stirred for an additional 8 h at rt. The solvent was then removed under reduced pressure and the residue was taken up in 10 mL of H_2O 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 to afford the crude amide **9** as a gum, which was purified by chromatography and/or crystallization.

2(*R*),3(*R*)-Dimethyl-4-pentynoic Acid Amide (9b). This material was prepared in 89% yield from 8.7 mmol of 2(*R*),3-(*R*)-dimethyl-4-pentynoic acid (**8b**),[1a] 1.0 equiv of NEt_3, and 1.0 equiv of isobutyl chloroformate by following the general procedure described above. Chromatography (silica gel, 20% EtOAc/hexanes) followed by crystallization (EtOAc) afforded 980 mg (89%) of **9b** as a colorless microcrystalline solid: mp 64−5 °C; R_f 0.52 (50% acetone/hexanes); $[\alpha]^{25}_D$ = 35.7° (*c* 16.75, MeOH); IR (CH_2Cl_2) 2933, 1736, 1463, 1375, 1200, 1090, 985, 912, 854 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 7.16 Hz, 3H), 1.29 (d, J = 7.16 Hz, 3H), 2.19 (d, J = 2.44 Hz, 1H), 2.42 (m, 1H), 2.77 (m, 1H), 5.46 (br s, 1H), 5.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 177.18, 86.58, 70.33, 45.68, 28.80, 17.70, 15.08. Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.91; H, 8.96; N, 11.08.

2(*S*),3(*S*)-Dimethyl-4-pentynoic Acid Amide (*ent*-9b). This material was prepared in 92% yield from 10.3 mmol of 2(*S*),3(*S*)-dimethyl-4-pentynoic acid (*ent*-**8b**),[1a] 1.0 equiv of NEt_3, and 1.0 equiv of isobutyl chloroformate by following the general procedure described above. Chromatography (silica gel, 20% EtOAc/hexanes) followed by crystallization (EtOAc) afforded 1.19 g (92%) of *ent*-**9b** as a colorless microcrystalline solid: mp 64−5 °C; $[\alpha]^{25}_D$ = −35.95° (*c* 14.13, MeOH); spectral data identical to those in **9b**.

2(*R*)-Methyl-3(*R*)-(1′(*S*)-methoxyethyl)-4-pentynoic Acid Amide (9c). This material was prepared in 90% yield from 1.46 mmol of 2(*R*)-methyl-3(*R*)-(1′(*S*)-methoxyethyl)-4-pentynoic acid (**8c**),[1a] 1.0 equiv of NEt_3, and 1.0 equiv of isobutyl chloroformate by following the general procedure described above. Chromatography (silica gel, 20% EtOAc/hexanes) followed by crystallization (EtOAc/hexanes) afforded 223 mg (90%) of **9c** as a colorless microcrystalline solid: mp 148−9 °C; R_f 0.71 (50% acetone/hexanes); $[\alpha]^{25}_D$ = −14.62° (*c* 3.01, MeOH); IR (CH_2Cl_2) 3520, 3403, 3302, 2983, 2986, 2348, 2687,

(21) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *Tetrahedron Lett.* **1995**, *36*, 1193.

1592, 1461, 1391, 1188, 1145, 1085, 1007, 960, 647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, $J = 6.7$ Hz, 3H), 1.32 (d, $J = 6.24$ Hz, 3H), 2.25 (d, $J = 2.4$ Hz, 1H), 2.64 (m, 2H), 3.37 (s, 3H), 3.50 (m, 1H), 5.38 (br s, 1H), 5.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 180.89, 83.25, 75.57, 73.54, 56.83, 43.40, 42.10, 17.29, 16.26. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.69; H, 8.85; N, 8.30.

2(*R*)-Methyl-3(*R*)-(1′(*S*)-(benzyloxy)ethyl)-4-pentynoic Acid Amide (9d). This material was prepared in 96% yield from 5.6 mmol of 2(*R*)-methyl-3(*R*)-(1′(*S*)-(benzyloxy)-ethyl)-4-pentynoic acid (**8d**),[1a] 1.0 equiv of NEt_3, and 1.0 equiv of isobutyl chloroformate by following the general procedure described above. Chromatography (silica gel, 30% acetone/hexanes) followed by crystallization (EtOAc/hexanes) afforded 1.32 g (96%) of **9d** as a colorless microcrystalline solid: mp 130−1 °C; R_f 0.74 (50% acetone/hexanes); $[\alpha]^{25}_D = -52.26°$ (*c* 2.13, MeOH); IR (CH_2Cl_2) 3377, 3283, 3201, 2966, 2892, 2343, 1642, 1613, 1454, 1343, 1278, 1143, 1102, 1049, 743, 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (d, $J = 6.24$ Hz, 3H), 1.37 (d, $J = 6.2$ Hz, 3H), 2.25 (d, $J = 1.76$ Hz, 1H), 2.64 (m, 2H), 3.70 (m, 1H), 4.56 (A,B-q, $J = 11.88$ Hz, 2H), 5.40 (br s, 1H), 5.85 (br s, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 177.47, 138.11, 128.32 (2), 127.97 (2), 127.68, 82.35, 72.75, 72.24, 70.57, 42.37, 41.73, 17.55, 15.99. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.20; H, 7.87; N, 5.63.

2(*S*)-Methyl-3(*S*)-(1′(*R*)-(benzyloxy)ethyl)-4-pentynoic Acid Amide (*ent*-9d). This material was prepared in 96% yield from 5.6 mmol of 2(*S*)-methyl-3(*S*)-(1′(*R*)-(benzyloxy)ethyl)-4-pentynoic acid (*ent*-**8d**),[1a] 1.0 equiv of NEt_3, and 1.0 equiv of isobutyl chloroformate by following the general procedure described above. Chromatography (silica gel, 30% acetone/hexanes) followed by crystallization (EtOAc/hexanes) afforded 1.32 g (96%) of *ent*-**9d** as a colorless microcrystalline solid: mp 130−1 °C; $[\alpha]^{25}_D = 51.6°$ (*c* 2.19, MeOH); spectral data identical to those in **9d**.

***N*-Benzyl-4-pentynoic Acid Amide (9e).** A solution of 536 mg (5.0 mmol) of benzylamine and 491 mg (5.0 mmol, 1.0 equiv) of 4-pentynoic acid (**8a**)[1a] in 15.0 mL of anhydrous THF was treated with 1.92 g (10.0 mmol, 2.0 equiv) of EDCI, and the resulting mixture was stirred vigorously at rt for 28 h. At the end of this period the reaction mixture was concentrated and partitioned between 10 mL of H_2O and 25 mL of CH_2Cl_2, and the aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 966 mg of a light yellow gum. Flash chromatography (silica gel, 20% EtOAc/hexanes) then gave 902 mg (96%) of **9e** as a colorless microcrystalline solid: mp 65−6 °C (pentane); R_f 0.48 (30% EtOAc/hexanes); IR (KBr) 3276, 1652, 1560, 1455, 1431, 1265, 1182, 1082, 748, 696, 645, 609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (t, $J = 2.76$ Hz, 1H), 2.43 (m, 2H), 2.55 (m, 2H), 4.45 (d, $J = 5.6$ Hz, 2H), 5.85 (br s, 1H), 7.29 (m, 5H). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.30; H, 6.89; N, 7.43.

1-Carbomethoxy-4,5,6,7-tetrahydro-2*H*-isoindole (16). A solution of 6.41 g (54.4 mmol) of 1-nitrocyclohexene (**13**) and 5.0 g (54.4 mmol, 1 equiv) of methyl isocyanoacetate (**14**) in 60 mL of anhydrous THF was cooled to 0 °C with stirring and was treated with 8.28 g (54.4 mmol, 1 equiv) of DBU. After the addition was complete, the reaction mixture was allowed to warm to rt and stirring was continued for 12 h. The resulting solution was then poured over 100 g of crushed ice containing 25 mL of 1 N HCl. After melting, the aqueous solution was extracted with 3 × 20 mL of EtOAc, and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 12.08 g of crude **16** as a honey-colored solid. Purification by flash chromatography (silica gel, 20% EtOAc/hexanes) then gave 7.30 g (75%) of **16** as a colorless crystalline solid: mp 94−5 °C (EtOAc/hexanes); R_f 0.77 (30% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 1.73 (br m, 4H), 2.53 (t, 2H), 2.79 (t, 2H), 3.82 (s, 3H), 6.66 (d, 1H), 8.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 162.00, 128.22, 122.00, 118.99, 117.36, 50.98, 23.35, 23.28, 23.03, 21.86. Combustion analysis was performed on iodo derivative **17**.

1-Carbomethoxy-3-iodo-4,5,6,7-tetrahydro-2*H*-isoindole (17). A solution of 1.75 g (9.77 mmol) of isoindole **16** in 20 mL of anhydrous THF was treated at rt with 4.40 g (19.54 mmol, 2 equiv) of *N*-iodosuccinimide, and the resulting dark solution was stirred at rt for 2.5 h. The reaction mixture was then concentrated under reduced pressure, and the residue was taken up in 25 mL of H_2O and extracted with 3 × 20 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to give 2.65 g (89%) of **17** as an off-white crystalline solid: mp 186−9 °C (EtOAc/hexanes); R_f 0.75 (30% EtOAc/hexanes); IR (KBr) 3266, 2940, 1671, 1554, 1435, 1394, 1320, 1233, 1133, 1033, 957, 814, 768, 723, 598 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 160.56, 129.50, 127.92, 122.79, 71.50, 51.37, 23.43, 23.17, 23.12, 23.07. Anal. Calcd for $C_{10}H_{12}NO_2I$: C, 39.37; H, 3.96; N, 4.59. Found: C, 39.43; H, 4.01; N, 4.54.

1-Carbomethoxy-3-(2′-phenylethynyl)-4,5,6,7-tetrahydro-2*H*-isoindole (19). A solution of 100 mg (0.33 mmol) of iodoisoindole **17**, 36.8 mg (0.36 mmol, 1.1 equiv) of acetylene **18**, 38.0 mg (0.033 mmol, 0.1 equiv) of $Pd(Ph_3P)_4$, and 13.73 mg (0.072 mmol) of CuI in 3.0 mL of dry DMF was prepared in a drybox, purged thoroughly with argon, and treated *via* syringe with 137.8 μL (0.99 mmol, 3 equiv) of freshly distilled Et_3N. The reaction mixture was then cooled in liquid nitrogen, and the frozen solid was subjected to five freeze−thaw cycles before being warmed to rt under an atmosphere of argon and being stirred for 21 h. At the end of this period, the dark reaction mixture was concentrated under reduced pressure, and the residue was taken up in 50 mL of CH_2Cl_2. The CH_2Cl_2 was filtered through a short pad of Celite to remove the catalyst and was then stirred with 5 mL of saturated $NaHCO_3$ for 15 min. The organic layer was separated, washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5−30% EtOAc/hexanes) afforded 74.5 mg (89%) of **19** as a colorless gum, which crystallized from EtOAc/pentanes as a colorless microcrystalline solid: mp 193−4 °C; R_f 0.78 (30% EtOAc/hexanes); IR (KBr) 3283, 2939, 2203, 1675, 1599, 1580, 1491, 1403, 1293, 1217, 1197, 1151, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (m, 4H), 2.62 (m, 2H), 2.79 (m, 2H), 3.85 (s, 3H), 7.33−7.49 (m, 5H), 8.90 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 161.28, 131.22, 128.32, 128.30, 127.72, 122.71, 118.19, 113.71, 94.35, 80.26, 51.26, 23.03, 22.97, 22.87, 21.80. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.32; H, 6.14; N, 4.95.

Pyrroloalkyne 20a. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 1.0 mmol of iodopyrrole **17**, 1.3 mmol (1.3 equiv) of alkyne **9a**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (silica gel, 50% acetone/hexanes) afforded 246 mg (88%) of **20a** as a colorless microcrystalline solid: mp 282−3 °C; R_f 0.29 (50% acetone/hexanes); IR (CH_2Cl_2) 3435, 3074, 1727, 1680, 1551, 1409, 1298, 1150, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (br m, 4H), 2.51 (br m, 2H), 2.54 (m, 2H), 2.76 (br m, 2H), 2.82 (m, 2H), 3.83 (s, 3H), 5.35 (br s, 1H), 5.56 (br s, 1H), 8.69 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 173.36, 159.73, 128.31, 125.62, 124.83, 81.32, 72.85, 51.51, 34.82, 28.40, 21.31, 11.78. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.07; H, 6.59; N, 10.07.

Pyrroloalkyne 20b. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 1.37 mmol of iodopyrrole **17**, 1.70 mmol (1.25 equiv) of alkyne **9b**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (50% acetone/hexanes) afforded 399 mg (96%) of **20b** as a colorless microcystalline solid: mp 272−3 °C; R_f 0.58 (50% acetone/hexanes); $[\alpha]^{25}_D = 35.1°$ (*c* 2.9, MeOH); IR (CH_2Cl_2) 3296, 2850, 1685, 1636, 1560, 1458, 1267, 773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, $J = 7.1$ Hz, 3H), 1.29 (d, $J = 7.0$ Hz, 3H), 1.72 (m, 4H), 2.45 (m, 1H), 2.49 (m, 2H), 2.74 (m, 2H), 2.98 (m, 1H), 3.82 (s, 3H), 5.40 (br s, 1H), 5.76 (br s, 1H), 8.80 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 175.39, 160.42, 127.15, 125.37, 116.78, 114.21, 97.89, 72.74, 50.76, 45.79, 44.25, 29.09, 22.80, 21.31, 16.94, 13.78, 8.71; MS (EIMS) *m/z* 302 ($M^{+\bullet}$).

Pyrroloalkyne *ent*-20b. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 1.0 mmol of iodopyrrole **17**, 1.33 mmol (1.33 equiv) of alkyne *ent*-**9b**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (50% acetone/hexanes) afforded 298 mg (98%) of *ent*-**20b** as a colorlesss microcrystalline solid: mp 272−3 °C; R_f 0.58 (50% acetone/hexanes); $[\alpha]^{25}_D = -36.9°$ (*c* 5.2, MeOH); spectral data identical to those in **20b**.

Pyrroloalkyne 20c. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 0.49 mmol of iodopyrrole **17**, 0.59 mmol (1.2 equiv) of alkyne **9c**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (5−30% acetone/hexanes) afforded 151 mg (89%) of **20c** as a colorless microcrystalline solid: mp 188−9 °C (EtOAc/hexanes); R_f 0.54 (50% acetone/hexanes); $[\alpha]^{25}_D = -30.62°$ (*c* 2.32, MeOH); IR (CH_2Cl_2) 3050, 2936, 2858, 2253, 1689, 1530, 1460, 1376, 1343, 1247, 1180, 1150, 1094, 1030, 909, 548 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 6.88 Hz, 3H), 1.32 (d, J = 6.08 Hz, 3H), 1.68 (m, 4H), 2.46 (m, 2H), 2.73 (m, 3H), 2.83 (m, 1H), 3.34 (s, 3H), 3.54 (m, 1H), 3.78 (s, 3H), 5.44 (br s, 1H), 5.89 (br s, 1H), 8.97 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 177.92, 162.40, 127.93, 126.51, 117.07, 114.16, 92.51, 76.05, 56.44, 50.91, 42.65, 42.60, 36.39, 22.95, 22.75, 21.54, 17.08, 15.77; MS (EIMS) *m/z* 346 (M^+), 314, 270, 255, 244, 212, 170, 141, 115, 84; HRMS calcd for $C_{19}H_{26}O_4N_2$ 346.1894, found 346.1898. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.72; H, 7.62; N, 8.06.

Pyrroloalkyne 20d. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 0.91 mmol of iodopyrrole **17**, 1.0 mmol (1.1 equiv) of alkyne **9d**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (5−40% acetone/hexanes) afforded 422 mg (96%) of **20d** as a colorless solid: mp 188−9 °C (EtOAc/hexanes); R_f 0.33 (50% acetone/hexanes); $[\alpha]^{25}_D = -91.38°$ (*c* 5.45, MeOH); IR (CH_2Cl_2) 3686, 3436, 3073, 2940, 2859, 2358, 1700, 1604, 1459, 1343, 1179, 1152, 1088, 1028, 958, 908 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 3H), 1.47 (d, J = 6.2 Hz, 3H), 1.77 (m, 4H), 2.56 (m, 2H), 2.80 (m, 3H), 2.94 (m, 1H), 3.83 (m, 1H), 3.88 (s, 3H), 4.63 (A,B-q, J = 11.72 Hz, 2H), 5.48 (br s, 1H), 5.93 (br s, 1H), 7.3−7.4 (m, 5H), 9.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 177.47, 161.31, 138.16, 128.34 (2), 127.95 (2), 127.72, 127.70, 127.01, 117.70, 114.01, 92.99, 75.99, 72.69, 70.59, 51.40, 42.98, 42.62, 23.06, 23.00, 22.90, 21.76, 17.84, 16.11; MS (EIMS) *m/z* 422 (M^+), 378, 360, 332, 314, 305, 287, 255; MS (CIMS) *m/z* 423 $(M + 1)^+$; HRMS calcd for $C_{25}H_{30}O_4N_2$ 422.2207, found 422.2238. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 70.93; H, 7.14; N, 6.50.

Pyrroloalkyne 20e. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 0.91 mmol of iodopyrrole **17**, 1.0 mmol (1.1 equiv) of alkyne **9e**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (30% acetone/hexanes) afforded 338 mg (92%) of **20e** as a colorless solid: mp 179−80 °C (EtOAc/hexanes); R_f 0.60 (50% acetone/hexanes); IR (CH_2Cl_2) 3440, 3043, 2980, 2858, 2359, 1684, 1516, 1459, 1343, 1179, 1152, 1098, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (m, 4H), 2.45 (m, 2H), 2.51 (t, J = 7.04 Hz, 2H), 2.76 (m, 2H), 2.83 (t, J = 7.04 Hz, 2H), 3.84 (s, 3H), 4.49 (d, J = 5.72 Hz, 2H), 5.87 (br s, 1H), 7.27 (m, 5H), 8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.74, 161.00, 137.95, 128.61 (2), 128.19, 127.68 (2), 127.49, 126.85, 117.34, 113.69, 93.56, 72.55, 51.14, 43.68, 35.61, 22.98, 22.93, 22.86, 21.67, 16.21. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.47; H, 6.70; N, 7.67.

Dihydropyrromethenone 21a. A solution of 34.0 mg (0.12 mmol) of pyrroloalkyne **20a** in 5 mL of anhydrous THF was treated with 0.72 mL (0.72 mmol, 6 equiv) of 1.0 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. The reaction mixture was then cooled in liquid nitrogen, and the frozen solution was subjected to five freeze−thaw cycles before being warmed to rt under an atmosphere of argon and, finally, being heated at reflux in an oil bath at 90 °C for 48 h. At the end of this period, the THF was evaporated under reduced pressure and the residue was taken up in 5 mL of H_2O and extracted with 3 × 10 mL of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a dark gum. Preparative TLC (silica gel, 50% acetone/hexanes) then afforded 8.5 mg (25%) of **21a** as a colorless solid: mp 272 °C (EtOAc); R_f 0.60 (50% EtOAc/hexanes); IR (CH_2Cl_2) 3430, 3310, 2938, 2858, 1715, 1683, 1572, 1498, 1307, 1168, 1146, 1083, 1052, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (br m, 4H), 2.40 (br m, 2H), 2.58 (t, J = 8.28 Hz, 2H), 2.78 (br m, 2H), 2.91 (t, J = 8.28 Hz, 2H), 3.80 (s, 3H), 5.28 (s, 1H), 8.46 (br s, 1H), 8.95 (br s, 1H); MS (EIMS) *m/z* 274 ($M^{+\bullet}$), 242, 214, 185, 91, 78, 63; MS (CIMS) *m/z* 275 $(M + 1)^+$; HRMS (EIMS) calcd for $C_{15}H_{18}O_3N_2$ 274.1317, found 274.1336. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 64.70; H, 6.70; N, 10.17.

Dihydropyrromethenone 21b. This material was prepared in a fashion identical to that of **21a** described above, using 55.0 mg (0.18 mmol) of pyrroloalkyne **20b**, 3.64 mL of anhydrous THF, and 1.09 mL (1.09 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (silica gel, 30% acetone/hexanes) afforded 44.6 mg (82%) of **21b** as a colorless solid: mp 266−7 °C; R_f 0.80 (50% acetone/hexanes); $[\alpha]^{25}_D$ = 41.55 (c 3.3, MeOH); spectral data identical to those of an authentic sample.[1a]

Dihydropyrromethenone *ent*-21b. This material was prepared in a fashion identical to that of **21a** described above, using 102.0 mg (0.34 mmol) of pyrroloalkyne *ent*-**20b**, 6.75 mL of anhydrous THF, and 2.03 mL (2.03 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (silica gel, 30% acetone/hexanes) afforded 81.6 mg (81%) of *ent*-**21b** as a colorless solid: mp 266−7 °C; R_f 0.80 (50% acetone/hexanes); $[\alpha]^{25}_D = -41.08$ (c 2.58, MeOH); spectral data identical to those of an authentic sample.[1a]

Dihydropyrromethenone 21c. This material was prepared in a fashion identical to that of **21a** described above, using 50.0 mg (0.14 mmol) of pyrroloalkyne **20c**, 3.5 mL of anhydrous THF, and 0.87 mL (0.87 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (silica gel, 30% acetone/hexanes) afforded 39.0 mg (78%) of **21c** as a yellow foam: R_f 0.77 (50% acetone/hexanes); $[\alpha]^{25}_D = -20.46°$ (*c* 6.84, MeOH); IR (CH_2Cl_2) 3437, 2931, 2821, 1732, 1686, 1591, 1497, 1455, 1366, 1298, 1238, 1189, 1083, 1018, 956, 809 cm^{-1}; ^1H 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), 3.82 (s, 3H), 3.58 (m, 1H), 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; MS (CIMS) *m/z* 347 $(M + 1)^+$; HRMS calcd for $C_{19}H_{26}O_4N_2$: 346.1892, found 346.1880. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.89; H, 7.60; N, 8.08.

Dihydropyrromethenone 21d. This material was prepared in a fashion identical to that of **21a** described above, using 90.0 mg (0.21 mmol) of pyrroloalkyne **20d**, 4.24 mL of anhydrous THF, and 1.3 mL (1.3 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (silica gel, 50% acetone/hexanes) afforded 67.5 mg (75%) of **21d** as a yellow foam: R_f 0.72 (50% acetone/hexanes); $[\alpha]^{25}_D$ = 8.14° (*c* 5.28, MeOH); IR (CH_2Cl_2) 3437, 1727, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6.3 Hz, 3H), 1.31 (d, J = 7.3 Hz, 3H), 1.70 (m, 4H), 2.35 (m, 2H), 2.50−2.70 (m, 2H), 2.75 (m, 2H), 2.97 (m, 1H), 3.73 (s, 3H), 4.56 (A,B-q, J = 11 Hz, 2H), 5.29 (s, 1H), 7.32 (m, 5H), 9.68 (br s, 1H), 9.97 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 182.31, 175.01, 162.98, 148.57, 139.06, 138.04, 130.37, 129.37 (2), 128.35, 128.30 (2), 121.42, 118.14, 93.47, 77.61, 71.57, 51.95, 51.77, 38.16, 24.09, 24.03, 22.65, 18.44, 16.01; MS (EIMS) *m/z* 422 (M^+), 314, 287, 244, 212, 184, 141, 105, 91; MS (CIMS) *m/z* 423 $(M + 1)^+$; HRMS calcd for $C_{25}H_{30}O_4N_2$ 422.2207, found 422.2238. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.89; H, 7.60; N, 8.08.

Dihydropyrromethenone 21e. This material was prepared in a fashion identical to that of **21a** described above, using 50 mg (0.14 mmol) of pyrroloalkyne **20e**, 2.75 mL of anhydrous THF, and 0.83 mL (0.83 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (silica gel, 30% acetone/hexanes) afforded 36.9 mg (73%) of **21e** as a colorless foam (1/1 mixture of *E*/*Z* isomers): R_f 0.77 (50% acetone/hexanes); IR (CH_2Cl_2) 3436, 3036, 2931, 2848, 1695, 1560,1490, 1443, 1401, 1337, 1237, 1202, 1149, 1084, 1031, 902, 820, 649, 520 cm^{-1}; ^1H NMR ($CDCl_3$) δ (combined 1:1 mixture of *E* and *Z* isomers) 1.70−1.90 (m, 8H), 2.18 (m, 2H), 2.38 (m, 2H), 2.60 (m, 1H), 2.75 (m, 2H), 2.75−3.00 (m, 7H), 3.10 (m, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 4.70 (s, 2H), 4.90 (s, 2H), 5.36 (s, 1H), 5.62 (s, 1H), 6.78 (m, 2H), 7.20−7.50 (m, 8H), 8.28 (br s, 1H), 8.52 (br s, 1H); MS (EIMS) *m*/*z* 364 ($M^{+\bullet}$), 273, 241, 242, 91 (base peak); MS (CIMS) *m*/*z* 365 $(M + 1)^+$; HRMS (EIMS) calcd for $C_{22}H_{24}O_3N_2$ 364.1818, found 364.1788. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.37; H, 6.63; N, 7.65.

Pyrroloalkyne 29. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 0.64 mmol of iodopyrrole **27**, 0.95 mmol (1.5 equiv) of alkyne **9d**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (30% acetone/hexanes) afforded 317 mg (97%) of **29** as a colorless microcrystalline solid: mp 156−7 °C (CH_2Cl_2/pentanes); R_f 0.57 (50% acetone/hexanes); $[\alpha]^{25}_D = -91.76°$ (*c* 1.82, MeOH); IR (KBr) 3343, 2977, 2933, 1736, 1675, 1617, 1454, 1368, 1345, 1273, 1167, 1135, 1057, 957, 846, 779, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, *J* = 6.84 Hz, 3H), 1.40 (d, *J* = 6.08 Hz, 3H), 1.55 (s, 9H), 2.04 (s, 3H), 2.50 (t, *J* = 8.44 Hz, 2H), 2.72 (m, 1H), 2.87 (m, 1H), 2.96 (t, *J* = 8.44 Hz, 2H), 3.67 (s, 3H), 3.79 (m, 1H), 4.44 (d, *J* = 11.72 Hz, 1H), 4.70 (d, *J* = 11.72 Hz, 1H), 5.32 (br s, 1H), 5.83 (br s, 1H), 7.30−7.40 (m, 5H), 8.88 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 177.87, 173.50, 160.14, 138.05, 128.25 (2), 128.00, 127.89 (2), 127.62, 124.63, 120.01, 114.93, 92.66, 80.96, 76.12, 72.54, 70.49, 51.42, 42.48, 42.40, 34.81, 28.30 (3), 20.32, 17.75, 15.87, 9.48; MS (EIMS) *m*/*z* 510 (M^+). Anal. Calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H, 7.50; N, 5.49. Found: C, 68.03; H, 7.47; N, 5.44.

Pyrroloalkyne *ent*-29. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 0.37 mmol of iodopyrrole **27**, 0.41 mmol (1.1 equiv) of alkyne *ent*-**9d**, 0.1 equiv of $Pd(Ph_3P)_4$, 0.2 equiv of CuI, and 3 equiv of NEt_3 in 5 mL of freshly distilled DMF. After workup, flash chromatography (5−30% acetone/hexanes) afforded 197 mg (94%) of *ent*-**29** as a colorless crystalline solid: mp 156−7 °C (EtOAc/hexanes); R_f 0.57 (50% acetone/hexanes); $[\alpha]^{25}_D = 91.34°$ (*c* 2.78, MeOH); spectral data identical to those of **29**.

Dihydropyrromethenone 30. This material was prepared in a fashion identical to that of **21a** described above, using 160.0 mg (0.31 mmol) of pyrroloalkyne **29**, 6.25 mL of anhydrous THF, and 1.88 mL (1.88 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (preparative TLC, 500 μm silica gel, 30% acetone/hexanes) afforded 139.5 mg (87%) of **30** as a yellow foam: R_f 0.81 (50% acetone/hexanes); $[\alpha]^{25}_D = 7.46°$ (*c* 13.94, MeOH); IR (CH_2Cl_2) 3060, 2983, 2835, 2322, 1733, 1676, 1550, 1418, 1371, 1248, 1157, 906 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.24 Hz, 3H), 1.32 (d, *J* = 7.38 Hz, 3H), 1.55 (s, 9H), 1.92 (s, 3H), 2.51 (m, 2H), 2.65 (m, 1H), 2.99 (m, 3H), 3.69 (s, 3H), 3.80 (m, 1H), 4.55 (d, *J* = 11.77 Hz, 1H), 4.63 (d, *J* = 11.77 Hz, 1H), 5.31 (d, *J* = 1.25 Hz, 1H), 7.38 (m, 5H), 8.11 (br s, 1H), 8.85 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 179.76, 172.07, 160.07, 138.96, 138.21, 129.05 (2), 128.49, 128.41, 128.18 (2), 119.99, 117.91, 92.42, 80.93, 76.00, 71.88, 70.78, 51.48, 50.86, 37.39, 35.01, 28.50 (3), 20.91, 17.85, 15.23, 9.27; MS (EIMS) *m*/*z* 510 (M^+), 454, 402, 346, 319, 313, 301; (CIMS) *m*/*z* 511 (M + 1); HRMS calcd for $C_{29}H_{38}N_2O_6$ 510.2760, found 510.2731.

Dihydropyrromethenone *ent*-30. This material was prepared in a fashion identical to that of **21a** described above, using 100.0 mg (0.20 mmol) of pyrroloalkyne *ent*-**29**, 3.92 mL of anhydrous THF, and 1.20 mL (1.20 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF in a 25 mL round bottom flask. After the mixture was heated at reflux for 48 h under argon, workup and chromatography (preparative TLC, 500 μm silica gel, 30% acetone/hexanes) afforded 78.0 mg (78%) of *ent*-**30** as a yellow foam: R_f 0.81 (50% acetone/hexanes); $[\alpha]^{25}_D = -7.54°$ (*c* 5.7, MeOH); spectral data identical to those of **30**.

2(*R*),4(*S*)-Dimethyl-3(*R*)-ethynyl-γ-butyrolactone (37). A solution of 3.64 g (14.78 mmol, 1.0 equiv) of acetylenic acid **36** in 120 mL of CH_2Cl_2 was treated at rt, with vigorous stirring, with 6.57 g (1.0 equiv) of P_4S_{10} under an atmosphere of nitrogen. The reaction mixture was then stirred at rt for a total of 40 h and diluted with 250 mL of H_2O, and the aqueous layer was extracted with 6 × 80 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow gum. Chromatography (20% EtOAc/hexanes) then gave 1.95 g (95%) of lactone **37** as a pale yellow solid, which crystallized from Et_2O/hexanes in the form of colorless needles: mp 44.5−5.5 °C; $[\alpha]^{25}_D$ −95.7° (*c* 12.2, CH_2Cl_2); MS *m*/*z* 138 (M^+), 123, 110, 94, 77. 66; IR (CH_2Cl_2) 3303, 2988, 2939, 1775, 1453, 1390, 1324, 1181, 1125, 1055, 1015, 948 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, *J* = 7.2 Hz, 3H), 1.53 (d, *J* = 6.3 Hz, 3H), 2.34 (d, *J* = 2.4 Hz, 1H), 2.84 (m, 1H), 3.35 (m, 1H), 4.50 (m, 1H). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.60; H, 7.33.

1-((*tert*-Butyldimethylsilyl)oxy)-2(*R*)-methyl-3(R)-(1′-(*S*)-hydroxyethyl)-4-pentyne (39). A suspension of 0.64 g (16.8 mmol, 1.2 equiv) of $LiAlH_4$ in 300 mL of anhydrous THF was treated in a dropwise fashion, with vigorous stirring, with a solution of 1.94 g (14.0 mmol, 1.0 equiv) of lactone **37** in 15 mL of THF under an atmosphere of argon. The reaction mixture was stirred for an additional 11 h at rt, and the reaction was then carefully quenched with 27.6 mL of 10% aqueous NaOH. The organic layer was decanted into a separatory funnel, and the remaining gel was extracted repeatedly with Et_2O. The combined organic extracts were washed with 150 mL of brine, dried over anhydrous $NaSO_4$, filtered, and concentrated under reduced pressure to afford a colorless gum. Chromatography (50% EtOAc/hexanes) then gave 1.88 g (94%) of diol **38** (not shown) as a colorless oil: $[\alpha]^{25}_D = 5.7°$ (*c* 4.0, CH_2Cl_2); MS *m*/*z* 127 (M^+ − Me), 124, 123, 109, 97, 94, 83, 79; IR (CH_2Cl_2) 3608, 3400, 3302, 2972, 2933, 2879, 2112, 1456, 1379, 1062, 1039, 859 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, *J* = 6.6 Hz, 3H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.98 (m, 1H), 2.24 (d, *J* = 2.4 Hz, 1H), 2.48 (m, 1H), 2.73 (bs, 2H), 3.53 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.79 (dd, *J* = 8.3, 11.2 Hz, 1H), 3.94 (dq, *J* = 2.0, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.1, 22.6, 38.9, 45.7, 65.0, 68.4, 74.1, 80.5; HRMS (CIMS) calcd for ($C_8H_{14}O_2$ + H) (M + H^+): 143.1072, found 143.1069.

A solution of 1.83 g (12.9 mmol, 1.0 equiv) of diol **38** in 100 mL of dry CH_2Cl_2 was treated sequentially with 2.15 mL (1.2 equiv) of NEt_3, 1.63 g (1.2 equiv) of TBDMSiCl, and 62.9 mg (0.04 equiv) of DMAP. The reaction mixture was then stirred under nitrogen for 18 h, washed with 50 mL of saturated NH_4-Cl, followed by 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale yellow oil. Chromatography (5% EtOAc/hexanes) then gave 2.72 g (82%) of **39** as a colorless oil: $[\alpha]^{25}_D$ 5.7° (*c* 24.8, CH_2Cl_2); MS *m*/*z* 241 (M^+ − Me), 223, 199, 183, 155, 139, 105, 75; IR (CH_2Cl_2) 3381, 3303, 2958, 2931, 2859, 2111, 1472, 1390, 1365, 1258, 1074, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.89 (m, 1H), 2.15 (d, *J* = 2.4 Hz, 1H), 2.42 (m, 1H), 3.51 (dd, *J* = 4.2, 10.5 Hz, 1H), 3.79 (dd, *J* = 7.8, 10.5 Hz, 1H), 3.88 (dq, *J* = 2.3, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5 (2), 16.9, 18.3, 22.0, 25.9 (3), 38.6, 45.6, 65.7, 67.8, 73.2, 81.2. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.35; H, 11.08.

1-((*tert*-Butyldimethylsilyl)oxy)-2(*R*)-methyl-3(R)-[1′-(*R*)-(((*N*,*N*-dimethylamino)thiocarbonyl)thio)ethyl]-4-pentyne (40). A solution of 2.90 g (2.0 equiv) of triphenylphosphine in 30 mL of of anhydrous toluene was cooled to 0 °C under nitrogen and was treated in a dropwise fashion, with vigorous stirring, with 2.0 equiv of DEAD to give a yellow solution. After the mixture was stirred for an additional 30 min at 0 °C, the resulting light yellow suspension was treated with a solution of 1.42 g (5.54 mmol, 1.0 equiv) of alcohol **39** and 1.70 g of Ziram in 8.0 mL of dry toluene. After being

stirred an additional 6 h at rt, the reaction mixture was treated with an additional 0.84 g (0.5 equiv) of Ziram and stirring at rt was continued for 16 h. The reaction mixture was then concentrated under reduced pressure and chromatographed (silica gel, 5−10% EtOAc/hexanes) to afford 772 mg (39%) of **40** as a nearly colorless oil: $[\alpha]^{25}_D$ 104.8° (*c* 6.3, CH_2Cl_2); MS *m*/*z* 359 (M^+), 244, 326, 302, 259, 239, 187, 178, 139, 121, 88; IR (CH_2Cl_2) 3303, 2957, 2931, 2858, 1479, 1472, 1376, 1256, 1146, 1095, 1057, 982, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.12 (d, J = 6.6 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H), 1.78 (M, 1H), 2.13 (d, J = 2.4 Hz, 1H), 2.86 (m, 1H), 3.36 (s, 3H), 3.53 (s, 3H), 3.60 (dd, J = 6.6, 9.8 Hz, 1H), 3.84 (dd, J = 3.3, 9.8 Hz, 1H), 4.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −5.3 (2), 14.9, 15.3, 18.4, 26.0 (3), 38.4, 39.6, 41.5, 45.1, 48.3, 66.6, 71.8, 84.0, 196.5; HRMS (CIMS) calcd for ($C_{17}H_{33}NOS_2Si$ + H) (M + H^+) 360.1851, found 360.1858.

2(*R*)-Methyl-3(*R*)-[1′(*R*)-(((*N*,*N*-dimethylamino)thiocarbonyl)thio)ethyl]-4-pentynoic Acid Amide (43). A solution of 739 mg (2.05 mmol, 1.0 equiv) of silylated alcohol **40** in 12.5 mL of 1% HCl in 95% EtOH was stirred at rt for a period of 12 h. The reaction was then neutralized by careful addition of solid $NaHCO_3$ until gas evolution ceased, dried over anhydrous Na_2SO_4, filtered with the aid of EtOAc, and concentrated under reduced pressure. Chromatography (20% EtOAc/hexanes) then afforded 504 mg (100%) of alcohol **41** as a colorless oil: $[\alpha]^{25}_D$ 147.4° (*c* 7.6, CH_2Cl_2); MS *m*/*z* 245 (M^+), 228, 212, 187, 157, 139, 121, 88; IR (CH_2Cl_2) 3618, 3458, 3301, 3046, 2970, 2932, 2877, 2111, 1498, 1452, 1377, 1256, 1147, 1036, 981 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 6.6 Hz, 3H), 1.48 (d, J = 7.2 Hz, 3H), 1.88 (m, 2H), 2.20 (d, J = 2.4 Hz, 1H), 2.91 (m, 1H), 3.37 (s, 3H), 3.54 (s, 3H), 3.68 (dd, J = 5.4, 11.1 Hz, 1H), 3.85 (dd, J = 4.8, 11.1 Hz, 1H), 4.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.6, 38.3, 40.4, 41.6, 45.2, 48.2, 66.8, 72.4, 83.8, 196.3; HRMS (CIMS) calcd for ($C_{11}H_{19}NOS_2$ + H) (M + H^+) 246.0986, found 246.0985.

A stirring solution of 324 mg (1.32 mmol, 1.0 equiv) of alcohol **41** in 9.0 mL of dry DMF was treated at rt with 1.74 g (3.5 equiv) of pyridinium dichromate, and the resulting mixture was stirred at rt for 48 h. The reaction mixture was then poured carefully into 40 mL of H_2O in a separatory funnel with the aid of 40 mL of EtOAc. The separated aqueous layer, which had pH = 5, was acidified to pH = 3.5 by the addition of 0.5 mL of 5 N HCl and was then extracted with 5 × 40 mL of EtOAc. The combined extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and chromatographed (75:25:0.3 hexanes/EtOAc/AcOH) to afford 280 mg (82%) of carboxylic acid **42** as a pale yellow solid. Crystallization from MeOH then gave **42** as colorless crystals: mp 167−71 °C; $[\alpha]^{25}_D$ 171.7° (*c* 4.1, CH_2Cl_2); MS *m*/*z* 259 (M^+), 226, 212, 182, 162, 139, 121, 88; IR (CH_2Cl_2) 3490−2500, 3302, 3072, 2975, 2934, 1749, 1714, 1498, 1454, 1378, 1254, 1146, 981 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 7.2 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H), 2.17 (d, J = 2.4 Hz, 1H), 2.71 (m, 1H), 3.30 (m, 1H), 3.36 (s, 3H), 3.53 (s, 3H), 4.34 (m, 1H). Anal. Calcd for $C_{11}H_{17}NO_2S_2$: C, 50.95; H, 6.61; N, 5.41. Found: C, 51.03; H, 6.64; N, 5.44.

A solution of 280 mg (1.08 mmol, 1.0 equiv) of carboxylic acid **42** in 15 mL of anhydrous THF was cooled to 0 °C under nitrogen and was treated with vigorous stirring with 0.15 mL (1.0 equiv) of NEt_3 and 0.14 mL of isobutylchlorofomate. The resulting white suspension was stirred at 0 °C for an additional 30 min, then cooled to −78 °C, and treated with ∼2 mL of liquid NH_3 which had been condensed in a graduated cylinder at −78 °C by being passed through a tube filled with NaOH pellets. After the addition was complete, the reaction mixture was allowed to warm slowly to rt and was then stirred at rt for 3.5 h. The reaction mixture was then diluted with 25 mL of H_2O and EtOAc, and the separated aqueous layer was extracted with 5 × 25 mL of EtOAc. The combined extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and chromatographed (33% EtOAc/hexanes) to afford 169 mg (60%) of amide **43** as a colorless solid. Crystallization from Et_2O/CH_2Cl_2 then gave **43** as colorless crystals: mp 167.5−8.0 °C; $[\alpha]^{25}_D$ 230.6° (*c* 8.1, CH_2Cl_2); MS *m*/*z* 138 (M^+ − $SCSNMe_2$), 122, 88, 76, 49, 44; IR (CH_2Cl_2) 3519, 3402, 3301, 2976, 2933, 1691, 1592, 1498, 1454, 1378, 1255, 1147, 1052, 981 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 6.9 Hz, 3H), 1.47 (d, J = 7.2 Hz, 3H), 2.23 (d, J = 1.8 Hz, 1H), 2.55 (m, 1H), 3.25 (m, 1H), 3.36 (s, 3H), 3.53 (s, 3H), 4.33 (m, 1H), 5.55 (br s, 1H), 5.77 (br s, 1H). Anal. Calcd for $C_{11}H_{18}N_2OS_2$: C, 51.13; H, 7.02; N, 10.84; S, 24.81. Found: C, 51.25; H, 7.01; N, 10.88; S, 24.71.

2(*R*)-Methyl-3(*R*)-[1′(*S*)-hydroxyethyl]-4-pentynoic Acid Amide (47a). A solution of 60.0 mg (0.43 mmol, 1.0 equiv) of lactone **37** in 1.0 mL of saturated NH_3/MeOH was stirred at rt under an atmosphere of argon for 24 h. At the end of this period, the reaction was concentrated under reduced pressure and the residue was crystallized from CH_2Cl_2 to afford 64.2 mg (95%) of **47a** as colorless needles: mp 140−2 °C; $[\alpha]^{25}_D$ −38.8° (*c* 1.04, MeOH); IR (KBr) 3349, 2976, 2360, 2341, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H), 2.23 (d, J = 7.2 Hz, 1H), 2.29 (s, 1H), 2.57−2.69 (m, 2H), 3.99 (m, 1H), 5.47 (br s, 1H), 5.78 (br s, 1H); ^{13}C NMR (CD_3OD) δ 16.65, 22.71, 43.99, 44.22, 66.34, 74.42, 83.51, 181.64. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.94; H, 8.48; N, 8.95.

2(*R*)-Methyl-3(*R*)-[1′(*S*)-hydroxyethyl]-4-pentynoic Acid *N*-(4′-Methoxybenzyl)amide (47b). A solution of 45.0 mg (0.32 mmol, 1.0 equiv) of lactone **37** in 0.5 mL of anhydrous THF was treated with 0.26 mL (1.95mmol, 6.0 equiv) of *p*-methoxybenzylamine, and the resulting solution was stirred at rt under argon for 6 days. At the end of this period, the reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (25% EtOAc/hexanes) to afford 80.5 mg (90%) of **47b** as a colorless crystalline solid: mp 113−4 °C; $[\alpha]^{25}_D$ 19.1° (*c* 1.59, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H), 2.17 (s, 1H), 2.29 (br s, 1H), 2.61 (m, 2H), 3.80 (s, 3H), 3.98 (m, 1H), 4.41 (m, 2H), 5.99 (br s, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.57, 22.72, 43.49, 43.80, 43.83, 55.80, 66.56, 74.08, 82.34, 114.46 (2), 129.66 (2), 131.01, 159.44, 175.42. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.62; H, 7.63; N, 5.14.

Pyrroloalkyne 48a. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 135.9 mg (0.88 mmol, 1.0 equiv) of acetylenic amide **47a**, 516.5 mg (1.31 mmol, 1.5 equiv) of iodopyrrole **27**, 4.0 mL of freshly distilled DMF, 0.4 mL (3.0 equiv) of NEt_3, 106.0 mg (0.09 mmol, 0.1 equiv) of $Pd(Ph_3P)_4$, and 33.0 mg (0.17 mmol, 0.2 equiv) of CuI. After workup, flash chromatography (silica gel, 50% acetone/hexanes) afforded 351.2 mg (95%) of **48a** as an off-white foam: $[\alpha]^{25}_D$ −43.1° (*c* 2.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.3 Hz, 3H), 1.37 (d, J = 6.3 Hz, 3H), 1.53 (s, 9H), 2.00 (s, 3H), 2.44−2.49 (m, 2H), 2.71−2.85 (m, 2H), 2.90−2.96 (m, 2H), 3.37 (d, J = 7.5 Hz, OH), 3.66 (s, 3H), 4.06 (m, 1H), 6.35 (br s, 1H), 6.40 (br s, 1H), 10.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.92, 16.59, 21.45, 22.84, 28.85 (3), 35.52, 43.55, 45.01, 51.90, 67.04, 77.63, 81.68, 92.34, 115.94, 120.83, 124.95, 128.16, 161.29, 174.03, 179.35; HRMS (FAB) calcd for ($C_{22}H_{32}N_2O_6$ + H) 421.2339, found 421.2346 (M + H^+).

Pyrroloalkyne 48b. This material was prepared in a fashion identical to that of pyrroloalkyne **19** described above, using 53.1 mg (0.14 mmol, 1.5 equiv) of iodopyrrole **27**, 24.8 mg (0.09 mmol, 1.0 equiv) of acetylenic amide **47b**, 1.0 mL of freshly distilled DMF, 0.04 mL (3.0 equiv) of NEt_3, 12.0 mg (0.01 mmol, 0.11 equiv) of $Pd(Ph_3P)_4$, and 3.4 mg (0.018 mmol, 0.2 equiv) of CuI. After workup, flash chromatography (silica gel, 25% hexanes/EtOAc) afforded 39.8 mg (82%) of **48b** as an off-white foam: $[\alpha]^{25}_D$ −17.4° (*c* 3.3, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3H), 1.37 (d, J = 6.3 Hz, 3H), 1.54 (s, 9H), 1.99 (s, 3H), 2.50 (m, 2H), 2.68 (m, 1H), 2.82 (dd, J = 7.8, 2.1 Hz, 1H), 2.97 (m, 2H), 3.18 (br, OH), 3.66 (s, 3H), 3.70 (s, 3H), 4.09 (m, 1H), 4.33 (m, 2H), 6.23 (t, J = 5.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.14, 16.71, 21.37, 22.98, 28.91 (3), 35.43, 43.57, 44.34, 45.15, 51.98, 55.68, 67.22, 77.45, 81.61, 92.45, 114.41 (2), 115.35, 120.89, 125.37, 128.28, 129.42 (2), 130.56, 159.45, 160.67, 174.09, 175.57; HRMS (FAB) Calcd for ($C_{30}H_{40}N_2O_7$ + H) 541.2914, found 541.2912 (M + H^+).

Dihydropyrromethenone 31a. This material was prepared in a fashion identical to that of **21a** described above, using 72.9 mg (0.17 mmol, 1 equiv) of pyrroloalkyne **48a**, 4.0

mL of anhydrous THF, and 1.04 mL (1.04 mmol, 6.0 equiv) of 1.0 M *n*-Bu_4NF solution in THF. After the mixture was heated at reflux under argon for 48 h, workup and purification by flash chromatography (25% hexanes/EtOAc) afforded 31.5 mg (43%) of **31a** as a yellow foam: $[\alpha]^{25}_D$ −43.3° (*c* 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.51 (s, 9H), 1.94 (s, 3H), 2.46−2.60 (m, 3H), 2.65 (m 1H), 2.98 (m, 2H), 3.68 (s, 3H), 3.97 (m, 1H), 5.40 (s, 1H), 8.01 (br s, 1H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.69, 17.97, 20.14, 21.52, 28.91 (3), 35.60, 39.81, 51.95, 54.76, 70.20, 81.53, 94.49, 118.63, 120.52, 129.01, 129.72, 138.94, 161.96, 174.14, 181.68; HRMS (FAB) calcd for ($C_{22}H_{32}N_2O_6$ + H) 421.2339, found 421.2346 (M + H^+).

Dihydropyrromethenone 31b. This material was prepared in a fashion identical to that of **21a** described above, using 55.4 mg (0.10 mmol, 1.0 equiv) of pyrroloalkyne **48b** in 2.0 mL of anhydrous THF and 28.6 mg (0.10 mmol, 1.0 equiv) of *n*-$Bu_4NF{\cdot}3H_2O$. After the mixture was heated at reflux under argon for 19 h, workup and purification by flash chromatography (33% hexanes/EtOAc) afforded 44.4 mg (80%) of **31b** as a pale yellow gum: $[\alpha]^{25}_D$ −54.4° (*c* 2.5, CH_2Cl_2); IR (KBr) 3267, 2975, 2932, 1688, 1650, 1613, 1514, 1439, 1250, 1175, 1137 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.0 Hz, 3H), 1.39 (d, J = 7.2 Hz, 3H), 1.60 (s, 9H), 1.83 (s, 3H), 2.55 (m, 2H), 2.61 (t, J = 8.4 Hz, 2H), 3.04 (t, J = 8.4 Hz, 2H), 3.69 (s, 3H), 3.76 (s, 3H), 4.21 (d, J = 15.0 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H), 5.33 (s, 1H), 6.55 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 8.21 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.23, 17.73, 21.24, 21.61, 29.07 (3), 35.50, 41.43, 44.00, 51.98, 52.89, 55.79, 69.84, 80.84, 99.55, 114.77 (2), 119.13, 119.58, 128.62, 128.73, 128.94 (2), 129.75, 140.29, 159.57, 161.32, 174.36, 178.03; HRMS (FAB) calcd for ($C_{30}H_{40}N_2O_7$ + H) 541.2914, found 541.2912 (M + H^+).

Dihydropyrromethenone 32b. A solution of 178.5 mg (0.67 mmol, 5.0 equiv) of Ph_3P in 2.0 mL of anhydrous THF was cooled to 0 °C under argon and was treated with 0.14 mL (0.67 mmol, 5.0 equiv) of diisopropyl azodicarboxylate. After the mixture was stirred for an additional 30 min at 0 °C, the resulting white suspension was treated sequentially with 76.9 mg (0.13 mmol, 1.0 equiv) of alcohol **31b** and 0.05 mL (0.67 mmol, 5.0 equiv) of AcSH in 3.0 mL of dry THF. The reaction mixture was then stirred for 1 h at 0 °C, and 1 h at rt, before being poured into cold saturated $NaHCO_3$ and being extracted with EtOAc. The combined extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The unstable Mitsunobu product thus obtained was partly purified by flash chromatography (silica gel, 90% CH_2Cl_2/EtOAc) and was then dissolved in a solution consisting of 1.0 mL of CH_2Cl_2 and 1.0 mL of CF_3CO_2H. This solution was stirred under argon at rt for 3 h to effect *tert*-butyl ester hydrolysis. The reaction mixture was then treated with 1.0 mL of $CH(OCH_3)_3$ and stirred for an additional 10 min at rt, after which the resulting solution was poured over ice and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$, followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (33% hexanes/EtOAC) afforded 44.1 mg (62%) of **32b** as a pale yellow gum: $[\alpha]^{25}_D$ −54.4° (*c* 2.5, CH_2Cl_2); IR (KBr) 3256, 2954, 1720, 1696, 1618, 1514, 1440, 1347, 1248, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7.2 Hz, 3H), 1.37 (d, J = 7.5 Hz, 3H), 1.82 (s, 3H), 2.09 (s, 3H), 2.52 (m, 1H), 2.58 (t, J = 8.1 Hz, 2H), 3.02 (t, J = 8.1 Hz, 2H), 3.05 (m, 1H), 3.61 (m, 1H), 3.67 (s, 3H), 3.79 (s, 3H), 4.49 (d, J = 15.0 Hz, 1H), 4.89 (d, J = 15.0 Hz, 1H), 5.55 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 9.13 (br s, 1H), 9.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.43, 19.29, 19.90, 21.05, 31.05, 35.99, 40.21, 42.42, 44.11, 48.74, 52.14, 55.80, 94.48, 114.57 (2), 120.38, 128.02, 129.25, 129.50 (5), 133.65, 134.49, 145.29, 159.62, 173.36, 176.89, 177.88, 194.07; HRMS (FAB) calcd for ($C_{28}H_{34}N_2O_6S$ + H) 527.2216, found 527.2218 (M + H^+).

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

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **31a**,**b**−**32b**, **37**−**43**, and **47a**,**b**−**48a**,**b** (19 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.

JO970289B