New Strategies for the Synthesis of Biologically Important Tetrapyrroles. The "B,C + D + A" Approach to Linear Tetrapyrroles

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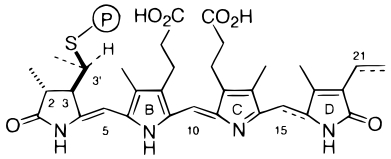
Linear tetrapyrroles related to phytochrome (**1**) were prepared in enantiospecific fashion by a new strategy beginning with ring-B,C synthons of type **19** (bis-iododipyrrins). Rings A and D were elaborated by Pd(0)-mediated coupling of **19a** with the appropriate alkyne acid or amide derivatives **9** and **20**, followed by intramolecular cyclization (method C: BC + D + A → ABCD).

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] and the phycocyanins (**2**) and phycoerythrins (**3**) (Figure 1).[8,9] Tetrapyrroles **2** and **3** are commonly found in blue-green, eucaryotic, and cryptomonad algae and serve as light harvesting proteins in photosynthesis. Phytochrome (**Pr**, **1**) plays an essential role in many light-dependent, irreversible processes, including seed germination, flowering, and stem growth. **Pr** has also been implicated in such reversible phenomena as chloroplast movement, root tip adhesion, potassium uptake, and regulation of transmembrane potentials.[2,6]



Phytochrome (**Pr**, **1**) (Δ-15, Δ-21)
Phycocyanin (**2**) (Δ-15)
Phycoerythrin (**3**) (Δ-21)

Figure 1.

The mechanism by which phytochrome (**1**) processes light signals has been the subject of intensive study, but it is still only poorly understood.[7a] An attractive approach to this problem involves the synthesis, and incorporation into the protein complex, of labeled derivatives of **1**.[10] This might enable the spectroscopic identification of geometrical changes induced by photochemical activation. However, synthetic efforts in this area are complicated by the instability of the chromophores, which rapidly decompose in the presence of base, light, or air. Until recently, it has not been possible to prepare derivatives of these materials in their free carboxylic acid form.[10b,c] In this paper, we describe a new strategy for the synthesis of linear tetrapyrroles that offers a potential solution to this problem.

Discussion and Results

Most linear tetrapyrrole syntheses have been carried out on simple model compounds and have utilized either of two synthetic strategies. The first of these is based on biosynthetic theory and involves the oxidative cleavage of porphyrins, chlorin, and related materials.[11] This

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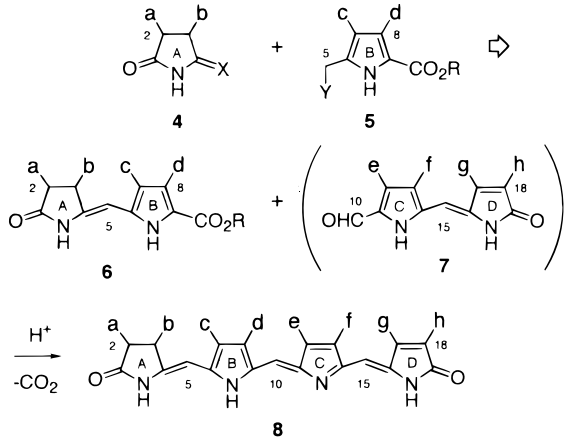
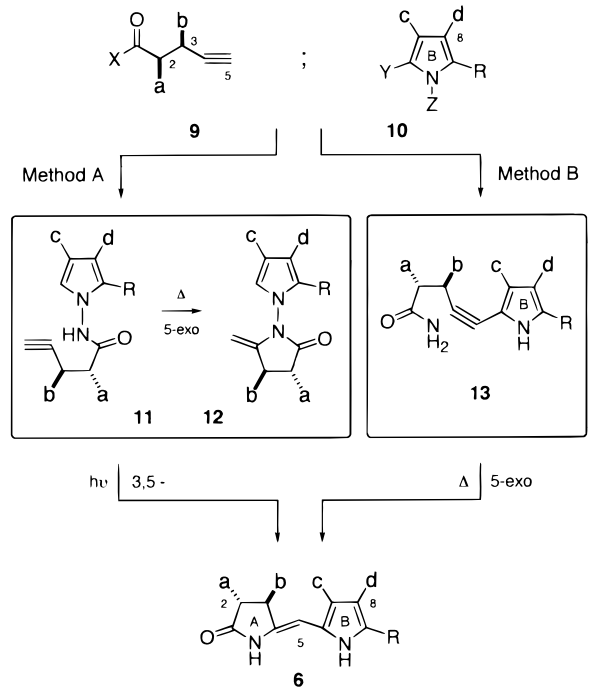
approach can sometimes be useful when applied to unsymmetrical tetrapyrroles. However, a more general strategy makes use of suitably functionalized pyrromethenone derivatives of type **6** and **7**, which can often be coupled to yield linear tetrapyrroles **8** in moderate to good yields (Scheme 1).[12] In principle, this approach affords good control over both stereo- and regiochemical features (a−h in **8**), as well as oxidation state at crucial ring positions. However, this "AB + CD" 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 not a trivial problem.[12a,b]

Scheme 1



Recently, we described two synthetic routes to highly substituted pyrromethenones of type **6**, each of which provided unambiguous control over both relative and absolute stereochemistry (Scheme 2).[13] In method A,[13a] *N*-pyrroloenamides of type **12** were prepared by a two-step sequence involving acylation of *N*-aminopyrroles **10a** (Y = H, Z = NH_2) with alkyne acids **9a** (X = OH), followed by 5-*exo*-*dig* cyclization of the resultant alkyne hydrazides **11**. Enamides **12**, upon 3,5-sigmatropic rearrangement, then afforded dihydropyrromethenones **6** containing all of the stereo- and regiochemical features found in rings A and B. In method B,[13b] alkyne pyrroles of type **13**, readily derived via Sonogashira coupling of iodopyrroles **10b** (Y = I, Z = H) with the appropriate alkyne amide **9b** (X = NH_2),[14] were directly converted to

Scheme 2



dihydropyrromethenones **6** by 5-*exo*-*dig* cyclization. A significant advantage of method B is the fact that bond connectivity between C_5 and C_6 is established directly, thereby eliminating the need for a subsequent 3,5-sigmatropic rearrangement. In addition, kinetic control in the amide addition to the alkyne triple bond leads directly to the naturally occurring *Z*-configuration at C_4−C_5 in **6**. Finally, an attractive feature of both methods A and B is that stereo- and regiochemical features incorporated into alkyne acid derivatives **9** are transposed in an unequivocal fashion to the final product **6**. As previously described,[13a,b] substrates of type **9** can be prepared in enantiomerically pure form using a Nicholas−Schreiber reaction.[15]

In practice, method A was not well suited for preparing sensitive substrates of the type required for the synthesis of tetrapyrroles such as **1**−**3**. Mainly this was due to the difficulty of finding protecting groups compatible with the photochemical rearrangement conditions.[13a] However, we did achieve considerable success with *Method B*, developing efficient syntheses of the enantiomerically pure ring-A,B dihydropyrromethenones **14**, **17a**,**b** (R = H, PMB) and **18**,[13b,e] as well as the ring-C,D pyrromethenone **15** (Scheme 3).[13c,d] Unfortunately, however, we obtained only trace amounts of tetrapyrrole **16** upon attempted acid-catalyzed coupling of **14** and **15**. Similarly, highly substituted dihydropyrromethenones of type **17** and **18** are unstable to the strongly acidic conditions required for condensation with **15** to afford tetrapyrroles.[13e]

Stability problems of this nature might be overcome with sufficient study. However, upon rethinking this issue, we concluded that a new strategy was required that would allow for incorporation of the most sensitive portion of the molecule at a later stage of the synthesis. In addition, we hoped to take advantage of the natural

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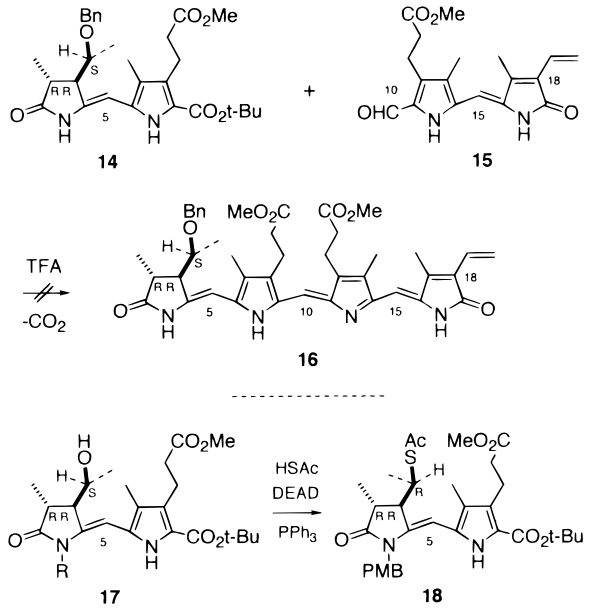
Scheme 3



symmetry associated with rings B and C in linear tetrapyrroles of type **1**−**3**. In Figure 2 we outline a conceptually new approach to the synthesis of linear tetrapyrroles (method C) that we believe has important advantages over the traditional AB + CD → ABCD methodology. As with methods A and B, method C takes advantage of a Nicholas−Schreiber reaction for preparing rings A and D in homochiral form and with unambiguous control over regiochemistry. However, a key precursor for method C is the ring-B,C dipyrrin **19**, which constitutes the most stable portion of the tetrapyrrole nucleus.[13f] We expected that sequential Pd(0)-mediated coupling of **19** with alkynes **20** and **9b** would afford bis-alkyne amides of general structure **21**, which should undergo cyclization to linear tetrapyrroles **22** under relatively mild conditions (vide supra). Concerning the coupling steps, it is important to note that **19** has a pseudoplane of symmetry (dotted line), since the pyrrole rings freely interconvert via tautomerization (Upon protonation, rings B and C are equivalent, as determined by NMR studies at low pH). Therefore, for the purpose of regiochemical control, it makes no difference which alkyne fragment is coupled first. For practical purposes, however, it would generally be best to add the less stable ring-A synthon last (BC + D + A → ABCD).

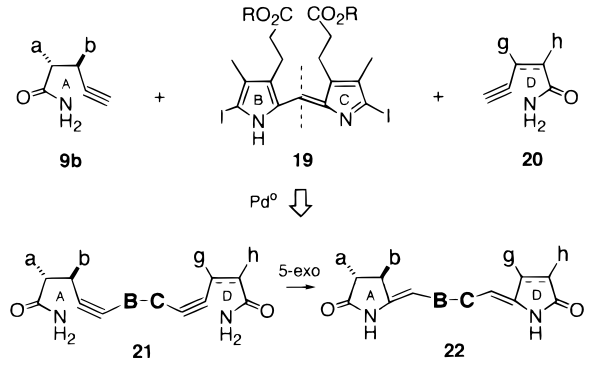
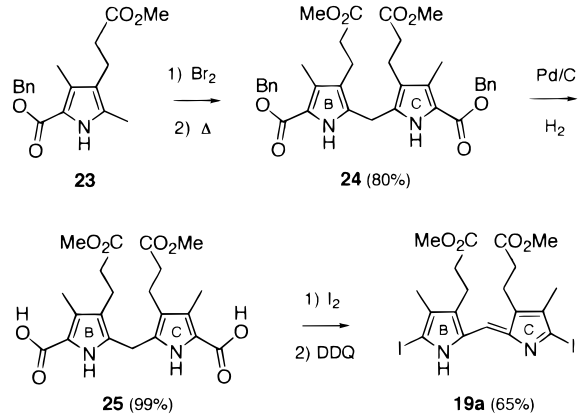


Figure 2.

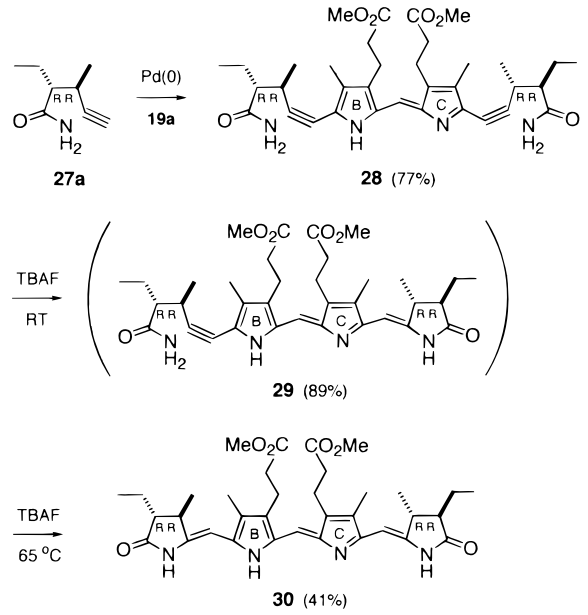
To explore this route, we first developed an efficient synthesis of the bis-iodo derivative **19a** (R = Me), which can be carried out on multigram scales beginning with the readily available pyrroloester **23** (Scheme 4).[12a] Following literature precedent,[16a] bromination of **23** in Et_2O, followed by brief heating in MeOH, afforded an 80% yield of dipyrrole **24** with no need for isolation of intermediates. This last material was then converted to the known bis-iododipyrromethane **26** (not shown) in 86% overall yield by a two step sequence involving catalytic hydrogenation to give the bis-dicarboxylic acid **25** (99%),[16b] followed by decarboxylative iodination (80%).[16c] Finally, oxidation of **26** with DDQ gave a 78% yield of the desired dipyrrin **19a** as a stable, crystalline compound (63% overall yield from **24**).

Scheme 4



Our initial cyclization experiments were carried out with the symmetrical bis-alkyne amide **28**, which was prepared in 77% yield by Pd(0)-mediated coupling of bis-iodo derivative **19a** with excess homochiral alkyne amide **27a** (Scheme 5).[13a] As expected, **28** underwent a facile 5-*exo*-*dig* cyclization upon catalysis with $Bu_4N^+F^-$ (TBAF),[13b] affording an 89% yield of mono-cyclized intermediate **29** after 1.5 h at 25 °C (*Z* stereochemistry

Scheme 5

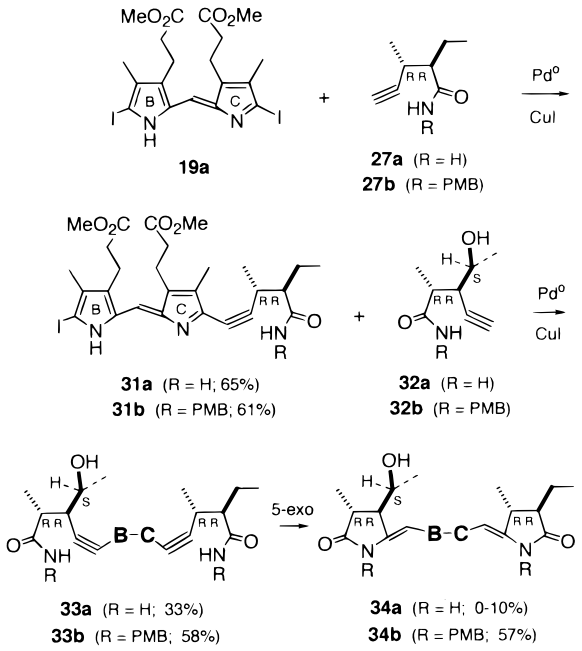


only; note that rings A and D are equivalent). Interestingly, however, cyclization of **29** to **30** was considerably slower, requiring 5 h at 65 °C for complete reaction (4

equiv of TBAF). In this case, we believe that cyclization of ring A is inhibited by the electron-donating ability of the ring D enamide functionality (cf. **29**), a point that will be discussed further below. In any event, we were sufficiently encouraged by these results to apply this same approach to unsymmetrical tetrapyrroles.

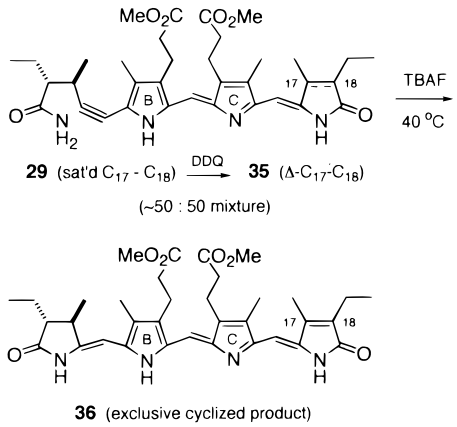
Following an analogous procedure, the unsymmetrical bis-alkyne amide **33a** was prepared by sequential coupling of **19a** first with the ring-D precursor **27a** (**19a** + **27a** → **31a**), followed by the less stable ring-A precursor **32a** (Scheme 6). As with the symmetrical bis-alkyne amide **28** (Scheme 5), mono-cyclization of **33a** was once again fast, affording a mixture of A- and D-ring cyclized tripyrroles after 1.5 h at 25 °C. However, the final cyclization to tetrapyrrole **34a** was very slow, affording only trace amounts of the desired product after 7 h at 65 °C (6 equiv of TBAF). This reaction was also accompanied by substantial decomposition. Much more satisfactory results were obtained with the bis-alkyne amide **33b** (R = *p*-methoxybenzyl),[13g] which was prepared in good overall yield by sequential Pd(0)-mediated coupling of **19a** with the *p*-methoxybenzyl amides **27b** (**19a** + **27b** → **31b**) and **32b**. Previously, we have observed that N-substitution can dramatically accelerate the rate of alkyne amide cyclization.[13g] This turned out to be especially true for **33b**, which afforded a 57% yield of tetrapyrrole **34b** after 1.5 h at 0 °C. By way of comparison, **33a** (R = H) was completely unreactive at this temperature, even after extended reaction periods. This route avoids the stability problems associated with the classical AB + CD strategy (cf. Scheme 3) and constitutes an efficient approach to tetrapyrroles in which *both* rings A and D are saturated.

Scheme 6



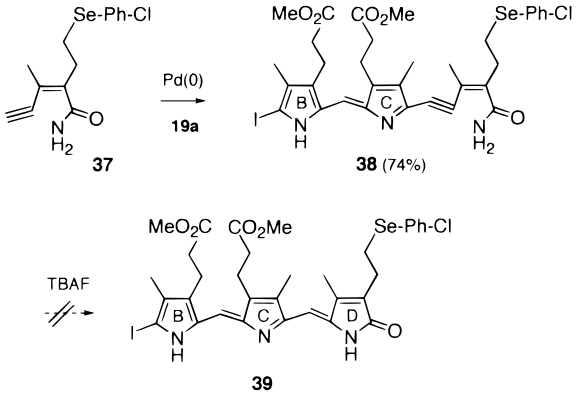
It was also of interest to explore the effect of ring D oxidation state on the rate of cyclization leading to ring A, since the natural tetrapyrroles **1**−**3** are unsaturated at C_{17}−C_{18}. These studies were carried out with alkyne amides **29** and **35**, which differ only in oxidation state at ring D (Scheme 7; **35** was generated in situ by DDQ oxidation of **29** and utilized as an ∼50:50 mixture). One would expect that cyclizations involving **35** (ΔC_{17}−C_{18}) would be fast relative to **29**, since the alkyne amide in **35** (but not in **29**) is conjugated with the electron-withdrawing carbonyl group in ring D. Therefore, it should be more susceptible to internal nucleophilic attack. This in fact turned out to be the case. Thus, in competition experiments, **29** (saturated C_{17}−C_{18}) was completely unreactive toward cyclization to **30** with TBAF at 40 °C (see also Scheme 5). Under identical conditions, however, **35** (ΔC_{17}−C_{18}) was rapidly converted to tetrapyrrole **36** having the natural oxidation state of phycocyanin (**2**) (TLC).

Scheme 7



Based upon these results, we were optimistic that B,C,D-ring systems of type **39** could be versatile precursors to tetrapyrroles related to phytochrome (**1**) (Scheme 8). Along these lines, the requisite precursor **38** was readily prepared by Pd(0)-mediated coupling of alkyne amide **37**[13d] with the bis-iododipyrrin **19a** (74%). Surprisingly, however, alkyne amide **38** suffered only rapid decomposition upon attempted 5-*exo*-*dig* ring closure with TBAF. This outcome was partly due to the lability of the phenylselenide group.

Scheme 8



More promising results were obtained with the conjugated derivative **41** (Scheme 9), which was synthesized in low yield by Pd(0)-mediated coupling of **19a** with the corresponding unsaturated alkyne amide **40b** (15%, not shown)[13c] or, more efficiently, by peracid induced elimination of *p*-Cl-Ph-SeOH from **38** (70%). Although unstable to TBAF, alkyne amide **41** cyclized readily upon

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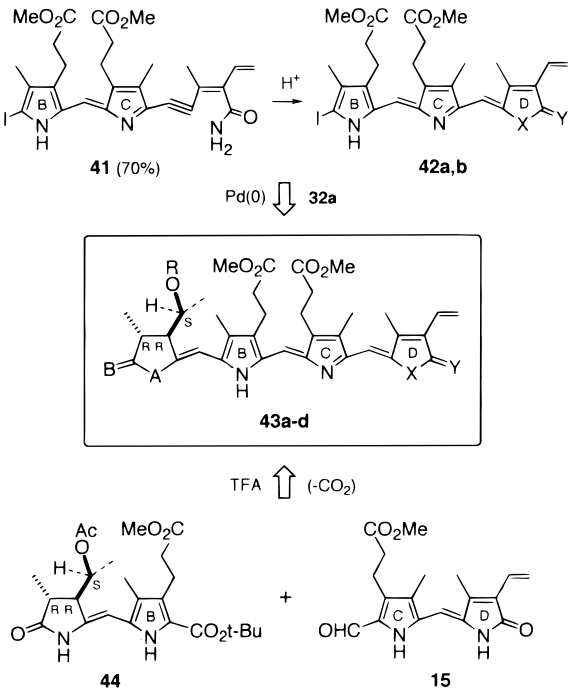
Scheme 9



a) A,X=NH; B,Y=O; R=H. **b**) A,X=O; B,Y=NH; R=H.
c) B=NH; A,X,Y=O; R=H. **d**) A,X=NH; B,Y=O; R=Ac.

acid catalysis, affording a 32% yield of a product **42** that had all of the analytical and spectroscopic properties expected for the tricyclic lactam **42a** (X = NH; Y = O). On this basis, **42** was coupled with the ring-A alkyne amide **32a**, and we were pleased to find that this reaction afforded a tetracycle **43** directly (R = H; 63%). Once again, **43** had the spectral properties anticipated for the phytochrome precursor **43a** (A,X = NH; B,Y = O; R = H) and upon acylation gave an *O*-acyl derivative **43**-*Ac* (R = Ac). However, tetracycle **43**-*Ac* thus prepared had different chromatographic and NMR spectra from authentic tetrapyrrole **43d** (A, X = NH; B, Y = O; R = Ac), which was synthesized in very low yield by decarboxylative condensation of pyrromethenones **44** and **15**. After lengthy studies, including X-ray analysis,[17] this discrepancy was traced to the fact that the initial acid-catalyzed cyclization of alkyne amide **41** had in fact given the iminolactone **42b** (X = O; Y = NH). From among many examples, this was the first time we observed this reaction pathway, which appears to require extended conjugation. For example, acid-catalyzed cyclization does not occur with tetrahydro substrates such as **28** (Scheme 5) or even dihydro substrates of type **38** (Scheme 8). These observations are consistent with a mechanism involving protonation of **41** to give the relatively stable, delocalized cation **41**-H^+, followed by capture with the "hard" amide oxygen (Figure 3).[18] Finally, Pd(0)-induced

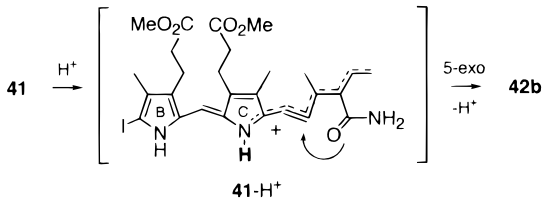
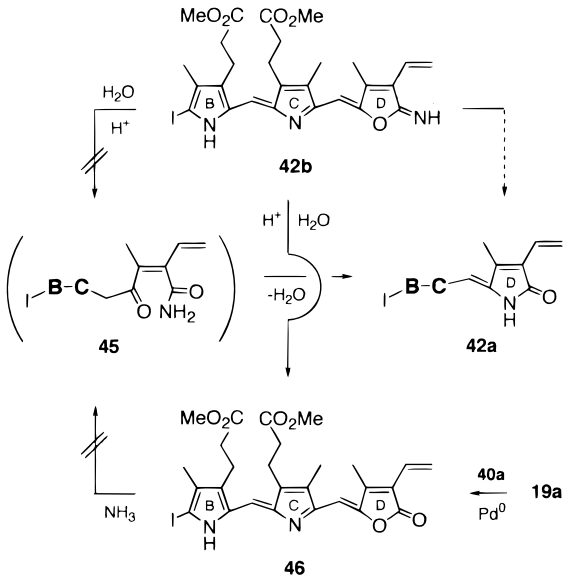


Figure 3.

coupling/cyclization of ring A also occurred with oxo-selectivity, affording tetrapyrrole **43c** (B = NH; A, X, Y = O; R = H) following hydrolysis of ring-D (Scheme 9). The identity of **43c** was confirmed by direct coupling/cyclization of lactone **46** (see below) with the alkyne amide **32a**. Oxo-selectivity of this type has been observed previously with chelating substrates.[13h,i]

Considerable effort was devoted to altering the chemoselectivity in the cyclization of **41** to **42**, which exhibited a small solvent effect. For example, variable amounts of the desired **42a** could be obtained when cyclization was carried out in CH_3CN/TsOH, as opposed to CH_2Cl_2/TsOH (100% **42b**). However, these results were generally unsatisfactory. We also explored two routes for converting the iminolactone **42b** to the desired lactam **42a** (Scheme 10). In principle, one means for converting **42b** to **42a** would make use of a Dimroth rearrangement, in which ring opening of **42b** to the keto-amide **45** is followed by cyclodehydration (**42b** → **45** → **42a**). Alternatively, acid-catalyzed hydrolysis of **42b** could lead directly to the tricyclic lactone **46**. In that case, reaction of **46** with NH_3 might then give the keto-amide **45**, which upon cyclodehydration would afford the desired lactam **42a**. Precedent exists for both pathways.[13h−j] In practice, however, attempted rearrangement of **42b** gave only trace amounts of the tricyclic lactam **42a**, and the major product was lactone **46**. The structure of **46** was confirmed by Pd(0)-mediated coupling of the dipyrrin **19a** with the corresponding unsaturated alkyne acid **40a** (not shown), followed by acid-catalyzed cyclization.[19] Also, the identical lactone **46** could be obtained directly from the alkyne amide **41** upon cyclization in the presence of equivalent amounts of H_2O (50% yield). This last method proved to be the most convenient. Unfortunately, however, all attempts at reacting **46** with NH_3 led to extensive decomposition, and no keto-amide **45** could be detected.

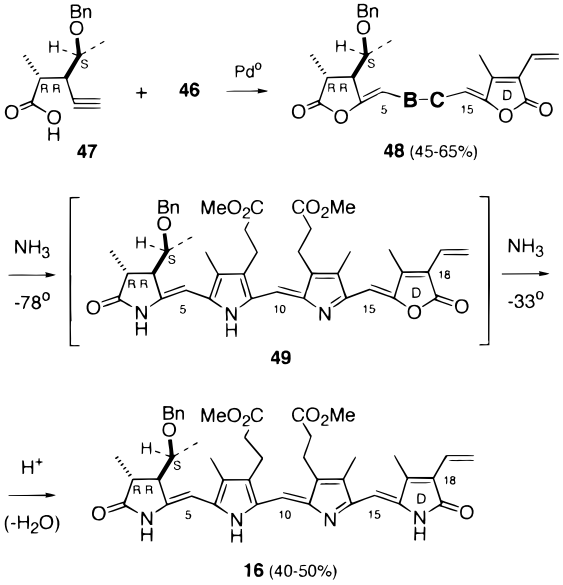
Scheme 10



Because of the instability of the iodolactone **46**, we elected to postpone ring opening until after formation of the tetrapyrrole. As summarized in Scheme 11, this strategy worked well. Thus, Pd(0)-catalyzed coupling of **46** with the alkyne acid **47** took place with concomitant cyclization, affording a 45−65% yield of the bis-lactone **48** (all *Z*-isomer only). In contrast to **46**, **48** reacted

cleanly with liquid NH_3 at −78 °C to afford the ring-A lactam **49**. In this case, initial ring opening was followed by spontaneous cyclodehydration. However, reaction at ring-D in **49** proved to be considerably slower and required 6−8 h at −33 °C, followed by acid-catalyzed cyclodehydration (40−50% overall yield). This route to **16** has clear advantages over the original AB + CD approach (cf. Scheme 3), in which the instability of the starting dihyropyrromethenone **14** precluded decarboxylative condensation.

Scheme 11



3′-Ethers of type **16** are of interest not only as possible precursors to phytochrome (**Pr**, **1**) and analogues, but also because they might be converted to enantiomerically pure 2*R*-phytochromobilin (**PΦB**, **50**).[20] This material can be isolated in trace amounts upon pyrolysis of the native **Pr** protein−chromophore complex (Figure 4).[20b] Lagarias et al. have demonstrated that in vitro reconstitution of **PΦB** with its apoprotein **N**−**C** occurs in an autocatalytic fashion, affording **Pr** having identical photochemical properties as the native protein/chromophore complex.[10a] This discovery opens the possibility for incorporation of labeled **PΦB** to study the process of photomorphogenesis at the molecular level.[10]

Summary

In this paper, we describe a conceptually new approach to the synthesis of linear tetrapyrroles related to phytochrome (**1**) (method C, BC + D + A → ABCD, Figure 2). The utility of this strategy stems partly from the fact that a wide variety of enantiomerically pure alkyne acids **9a** (and *ent*-**9a**) can be synthesized employing the Nicholas−Schreiber reaction of chiral ester enolates with cobalt stabilized propargylic cations.[13,15] Acids **9a** and amides **9b** are versatile precursors for rings-A and -D of a range of tetrapyrroles. In addition, ring-C,D synthons of type **19** can be prepared with unequivocal control over regiochemistry. As a consequence, method C provides for excellent flexibility in the introduction of substituents a−h in tetrapyrroles of general structure **8**. Of equal importance, the reactions employed are sufficiently mild for the introduction of labile functionality of the type found in naturally occurring tetrapyrrole chromophores.

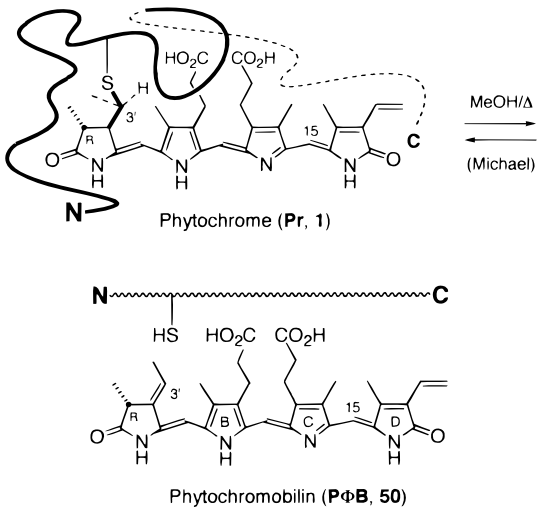


Figure 4.

Experimental Section

All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen or argon. Air- and moisture-sensitive compounds were introduced via syringe or cannula and weighed in a drybox. Reactions involving light-sensitive compounds were carried out wrapped in foil. Melting points are uncorrected and were measured on a Fisher-Jones melting point apparatus. Proton magnetic resonance spectra (^{1}H NMR) were recorded at either 300 or 400 MHz as indicated.

1,9-Diiodo-3,7-bis[2-(methoxycarbonyl)ethyl]-2,8-dimethyldipyrrin (19a). A total of 1.35 g (16.11 mmol, 7.0 equiv) of $NaHCO_3$ was added to a slurry of 1.00 g (2.30 mmol) of **25**[21] in H_2O (93 mL) and MeOH (30 mL). To this mixture was slowly added a solution of 1.16 g (4.60 mmol, 2.0 equiv) of iodine in 63 mL of MeOH. The resulting pink mixture became a brown slurry during the course of this addition. After vigorous stirring at room temperature, the mixture was placed into an ice bath and stirred for an additional 1.5 h at 0 °C. The product was filtered and washed sequentially with H_2O, saturated $NaHCO_3$ solution, H_2O, and hexanes. It was dried in vacuo for 24 h to give 1.1 g (80%) of the intermediate diiododipyrromethane **26** as a brown solid, which was dissolved in 110 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 500 mg (2.21 mmol, 1.2 equiv) of DDQ in one portion. The resulting solution was stirred at 0 °C for 10 min and diluted with saturated $NaHCO_3$ solution (100 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes/EtOAc/CH_2Cl_2, 4:1:1) afforded 715 mg (65%) of **19a** as an orange-brown solid: mp 140−41 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 6H), 2.52 (t, J = 7.8 Hz, 4H), 2.92 (t, J = 7.8 Hz, 4H), 3.66 (s, 6H), 6.66 (s, 1H). Anal. Calcd for $C_{19}H_{22}O_4N_2I_2$: C, 38.28; H, 3.72; N, 4.70; I, 42.57. Found: C, 38.38; H, 3.69; N, 4.66; I, 42.39.

(±)-*syn*-2-Ethyl-3-methylpent-4-yne Carboxamide (±-27a).[13c,22] A solution of 0.31 g (2.2 mmol, 1.1 equiv) of (±)-*syn*-2-ethyl-3-methylpent-4-yne carboxylic acid[22] in 35 mL of THF and 0.28 mL (2.0 mmol, 1.0 equiv) of Et_3N at 0 °C was treated under N_2, with vigorous stirring, with a total of 0.26 mL (2.0

(17) We are grateful to Dr. Victor G. Young, X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota, for carrying out the X-ray analysis of **42b** (cf. Supporting Information).

(18) See, for example, Ho, T.-L. *Tetrahedron* **1985**, *41*, 1

(19) We are grateful to Dr. Hui Liu of this department for carrying out these experiments.

(20) (a) Gossauer, A. *Tetrahedron* **1983**, *39*, 1933. (b) Rüdiger, W. *Struct. Bond.* **1980**, *40*, 101. See also ref 10a.

(21) Fuhrhop, J.-H.; Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam 1975; pp 761−764.

(22) DeSimone, R. W. Ph.D. Dissertation, Wesleyan University, Middletown, CT, 1992.

mmol, 1.0 equiv) of isobutyl chloroformate in a dropwise fashion over a period of 5 min. The resulting solution was stirred at 0 °C for 40 min. The solution was cooled to −78 °C, and NH_3, from NH_4OH dried through a $CaCl_2$ drying tube, was bubbled into the solution for 1 h. The reaction solution was allowed to warm to room temperature and stirred overnight. Solvent was removed under reduced pressure, the residue was taken up in 50 mL of H_2O and 50 mL of EtOAc and extracted with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, EtOAc) to afford 0.25 g (90%) of amide **(±)-27a**. Recrystallization from EtOAc/hexanes afforded this compound as colorless needles: mp 81−82 °C; R_f 0.61 (silica gel, EtOAc); IR (CCl_4) 3514.5, 3398.8, 3309.8, 2968.9, 2360.0, 1693.8, 1586.1, 1552.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 8.0 Hz, 3H), 1.35 (d, J = 7.0 Hz, 3H), 1.70−1.85 (m, 2H), 2.23 (m, 1H), 2.28 (d, J = 2.5 Hz, 1H), 2.83 (dt, J = 7.0, 3.0 Hz, 1H), 5.42 (br. s, 1H), 5.99 (br. s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.9, 18.4, 23.8, 27.7, 53.7, 70.7, 86.3, 176.6. Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 68.90; H, 9.38.

(2*R*,3*R*)-2-Ethyl-3-methylpent-4-yne Carboxamide (27a). This compound was prepared from the homochiral alkyne acid (2*R*,3*R*)-2-ethyl-3-methylpent-4-yne carboxylic acid[23] following a procedure identical to that described above for (±)-**27a**; identical spectral data as for (±)-**27a**.[13a−c]

(±)-*syn*-*N*-(4-Methoxybenzyl)-2-ethyl-3-methylpent-4-yne Carboxamide (±-27b). A total of 1.00 g (7.14 mmol, 1.0 equiv) of (±)-2-ethyl-3-methylpent-4-yne carboxylic acid[23] and 2 mL of oxalyl chloride (22.9 mmol, 3.2 equiv) were mixed and stirred for 7 h at room temperature. Excess oxalyl chloride was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). The resulting solution was added to an ice-cold solution of 4-methoxybenzylamine (4.7 mL, 36.0 mmol, 5.0 equiv) and Et_3N (3 mL, 21.5 mmol, 3 equiv) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min, poured into H_2O, and extracted with CH_2Cl_2. The organic extracts was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, EtOAc/hexanes 3:1) afforded 1.13 g (61%) of (±)-**27b** as colorless needles: R_f 0.28 (silica gel, EtOAc/hexanes 3:1); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.25 (d, 3H), 1.60−1.80 (m, 3H), 2.10 (m, 1H), 2.75 (m, 1H), 3.81 (s, 3H), 4.43 (d, 2H), 6.09 (br s, 1H), 6.87 (d, 2H), 7.25 (d, 2H).

(2*R*,3*R*)-*N*-(4-Methoxybenzyl)-2-ethyl-3-methylpent-4-yne Carboxamide (27b). This compound was prepared from the homochiral alkyne acid (2*R*,3*R*)-2-ethyl-3-methylpent-4-yne carboxylic acid[23] following a procedure identical to that described above for (±)-**27b**; identical spectral data as for (±)-**27b**.

Diamide 28. A mixture of 51 mg (0.086 mmol, 1 equiv) of **19a**, 47.6 mg (0.343 mmol, 4 equiv) of acetylenic amide **27a**, and 6.0 mg (0.0086 mmol, 0.1 equiv) of $PdCl_2(Ph_3P)_2$ in Et_3N (1.0 mL) and 1,4-dioxane (0.5 mL) was degassed by freeze−thaw cycle (three times) and then stirred at 50 °C under argon for 14 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography (3:2 hexanes/acetone) afforded 21.7 mg (77%) of **28** as an orange solid: mp 193−95 °C; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 6H), 1.33 (d, J = 6.9 Hz, 6H), 1.67 (m, 4H), 2.00 (s, 6H), 2.15 (m, 2H), 2.49 (t, J = 7.5 Hz, 4H), 2.86 (t, J = 7.5 Hz, 4H), 2.98 (m, 2H), 3.63 (s, 6H), 6.07 (br s, 2H), 6.70 (s, 1H), 7.45 (s,1H); ^{13}C NMR ($CDCl_3$) δ 10.3, 12.4, 19.1, 20.5, 24.3, 29.6, 35.7, 52.2, 54.7, 77.1, 101.3, 117.6, 129.5, 137.2, 137.9, 139.3, 173.6, 177.5. Anal. Calcd for $C_{35}H_{46}N_4O_6$: C, 67.94; H, 7.49; N, 9.05. Found: C, 67.82; H, 7.48; N, 8.99.

Amide 29. A solution of 20 mg (0.032 mmol, 1 equiv) of **28**, 0.26 mL (0.26 mmol, 8 equiv) of 1 M *n*-Bu_4NF solution in THF, and 0.2 mL of Et_3N in 2 mL of THF was purged with argon and stirred at room temperature under argon for 1.5 h. The reaction mixture was then diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/acetone) gave 17.8 mg (89%) of **29** as a purple solid: mp 53−5 °C; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.38 (d, J = 6.9 Hz, 3H), 1.64 (m, 3H), 1.85 (m, 1H), 2.01 (s, 3H), 2.05 (s, 3H), 2.18 (m, 1H), 2.38 (m, 1H), 2.51 (m, 4H), 2.89 (m, 5H), 3.01 (s, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 5.48 (s, 1H), 5.59 (br s, 1H), 6.63 (s 1H), 7.12 (br s, 1H), 8.5−9.2 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 10.21\, 10.2, 11.5, 12.7, 18.5, 20.0, 20.4, 20.5, 23.1, 24.2, 29.8, 30.0, 35.7, 35.9, 39.7, 50.3, 52.1, 54.4, 74.0, 92.2, 101.1, 113.3, 119.8, 125.5, 128.9, 130.4, 132.3, 143.5, 149.1, 153.9, 167.7, 173.6, 173.7, 177.3, 179.3; FAB HRMS, *m*/*z* 619.3487, M + H calcd for $C_{35}H_{47}N_4O_6$ 619.3496.

(2*R*,3*R*,17*R*,18*R*)-2,18-Diethyl-8,12-bis[2-(methoxycarbonyl)ethyl]-3,7,13,17-tetramethyl-2,3,17,18-tetrahydrobilin-1,19(21*H*,24*H*)-dione (30). A solution of 10 mg (0.016 mmol, 1 equiv) of **29** and 0.13 mL (0.13 mmol, 8 equiv) of 1 M *n*-Bu_4NF/THF in 0.5 mL of THF was purged with argon and heated at reflux under argon for 30 min. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/acetone) gave 4.1 mg (41%) of **30** as a purple solid: ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 6H), 1.44 (d, J = 6.9 Hz, 6H), 1.53−1.69 (m, 2H), 1.75−1.91 (m, 2H), 2.05 (s, 6H), 2.19−2.28 (m, 2H), 2.53−2.58 (m, 4H), 2.88−3.00 (m, 6H), 3.67 (s, 6H), 5.52 (s, 2H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.0, 11.8, 20.1, 20.6, 23.9, 36.0, 40.0, 49.8, 52.2, 91.1, 112.7, 125.6, 137.4, 138.6, 148.7, 150.2, 173.8, 179.5; FAB HRMS, *m*/*z* 619.34, M + H calcd for $C_{35}H_{47}N_4O_6$ 619.3496.

Amide 31a. A mixture of 102.8 mg (0.17 mmol, 2 equiv) of **19a**, 12 mg (0.086 mmol, 1 equiv) of the alkyne amide **27a**, and 12.0 mg (0.01 mmol, 0.12 equiv) of $Pd(Ph_3P)_4$ in Et_3N (1 mL) and 1,4-dioxane (0.5 mL) was degassed by freeze−thaw cycle (three times) and then stirred at 50 °C under argon for 11 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/acetone) afforded 34.0 mg (65%) of **31a** as an orange solid, which was recrystallized from EtOAc/hexane to give orange needles: mp 157−58 °C; ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.5 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.96 (s, 3H), 2.06 (s, 3H), 2.25 (m, 1H), 2.52 (m, 4H), 2.91 (m, 4H), 3.06 (m, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 5.50 (br s, 1H), 5.88 (br s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.6, 13.0, 18.7, 20.3, 20.7, 24.0, 29.8, 35.5, 35.6, 52.2, 52.2, 54.5, 74.9, 101.0, 117.1, 122.2, 125.9, 129.1, 131.2, 132.8, 134.9, 141.7, 149.4, 173.4, 173.5, 176.6. Anal. Calcd for $C_{27}H_{34}IN_3O_5$: C, 53.38; H, 5.64; N, 6.92. Found: C, 53.28; H, 5.68; N, 6.87.

Amide 31b. This material was prepared following a procedure identical to that described above for **31a**, using 381.2 mg (0.64 mmol, 2 equiv) of **19a**, 83.2 mg (0.32 mmol, 1 equiv) of the alkyne amide **27b**, 40.0 mg (0.034 mmol, 0.1 equiv) of $Pd(Ph_3P)_4$, 5 mL of Et_3N, and 2.5 mL of 1,4-dioxane. After the mixture was stirred at 50 °C under argon for 16 h, workup and purification by flash chromatography (1:1 hexanes/EtOAc) afforded 142.7 mg (61%) of **31b** as an orange-brown solid: ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.74 (m, 2H), 1.96 (s, 3H), 1.97 (s, 3H), 2.18 (m, 1H), 2.52 (m, 4H), 2.90 (m, 4H), 3.07 (m, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 4.45 (m, 2H), 6.04 (t, J = 5.4 Hz, 1H), 6.71 (s, 1H), 6.72 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.1, 12.7, 13.1, 10.0, 20.4, 20.7, 24.1, 30.0, 35.5, 35.6, 43.6, 52.2, 52.2, 55.2, 55.7, 75.0, 101.3, 114.5, 117.1, 122.3, 126.1, 129.2, 129.6, 131.0, 131.3, 132.8, 135.0, 141.7, 149.5, 159.4, 173.4, 173.5, 173.8; FAB HRMS, *m*/*z* 728.2196, M + H calcd for $C_{35}H_{43}IN_3O_6$ 728.2197.

Diamide 33a. A mixture of 70.0 mg (0.115 mmol, 1 equiv) of **31a**, 35.8 mg (0.23 mmol, 2 equiv) of the alkyne amide **32a**,[13b] and 15.0 mg (0.013 mmol, 0.11 equiv) of $Pd(Ph_3P)_4$ in Et_3N (1 mL), 1,4-dioxane (0.5 mL), and DMF (0.5 mL) was degassed by freeze−thaw cycle (three times) and then stirred at 50 °C under argon for 10 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (2:1, 1:1, 1:2 hexanes/acetone) afforded 24.0 mg (33%) of **33a** as an orange-brown

gum: $[\alpha]^{25}_D = -76°$ (*c* 1.1,CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 1.35 (d, J = 6.9 Hz, 3H), 1.42 (d, J = 6.3 Hz, 3H), 1.67 (m, 2H), 2.02 (s, 3H), 2.05 (s, 3H), 2.09−2.18 (m, 1H), 2.51 (t, J = 7.5 Hz, 4H), 2.73 (m, 1h), 2.88 (m, 4H), 2.98 (m, 1H), 3.65 (s, 6H), 4.02−4.10 (m, 1H), 4.9−5.4 (br, 2H), 5.97 (br s, 1H), 6.04 (br s, 1H), 6.73 (s, 1H), 7.54 (br s, 1H), 7.68 (br s, 1H); FAB HRMS, *m/z* 635.3450, M + H calcd for $C_{35}H_{46}N_4O_7$ 635.3445.

Diamide 33b. This material was prepared following a procedure identical to that described above for **33a**, using 153.2 mg (0.21 mmol, 1 equiv) of **31b**, 115.8 mg (0.42 mmol, 2 equiv) of alkyne amide **32b**,[13b] and 28.0 mg (0.024 mmol, 0.11 equiv) of $Pd(Ph_3P)_4$ in 4 mL of Et_3N and 2 mL of 1,4-dioxane. After the mixture was stirred at 50 °C under argon for 6 h, workup and flash chromatography (3:2 hexanes/acetone) afforded 106.3 mg (58%) of **33b** as an orange-brown solid: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6.3 Hz, 3H), 1.68 (m, 2H), 1.97 (s, 3H), 1.99 (s, 3H), 2.10 (m, 1H), 2.53 (m, 4H), 2.69 (m, 1H), 2.89 (m, 4H), 2.98 (m, 1H), 3.64 (s, 3H), 3.66 (s, 9H), 4.06 (m, 1H), 4.31−4.48 (m, 4H), 6.19 (t, J = 5.4 Hz, 1H), 6.28 (t, J = 5.4 Hz, 1H), 6.67 (m, 4H), 6.79 (s, 1H), 7.15 (m, 4H); FAB HRMS, *m/z* 875.4597, M + H calcd for $C_{51}H_{62}N_4O_9$ 875.4595.

Tetrapyrrole 34b. To a solution of 43.0 mg (0.049 mmol, 1 equiv) of **33b** in 4 mL of THF at 0 °C under argon was added 0.3 mL (0.3 mmol, 6 equiv) of 1 M *n*-Bu_4NF/THF, and the mixture was stirred at 0 °C under an argon atmosphere for 1.5 h. The reaction mixture was then diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo. Flash chromatography (2:1 hexanes/acetone) afforded 24.3 mg (57%) of **34b**: IR (KBr) 3432, 2963, 2933, 1722, 1656, 1623, 1595, 1514, 1438, 1346, 1248, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.38 (d, J = 7.5 Hz, 3H), 1.48 (m, 1H), 1.63 (m, 1H), 1.74 (s, 3H), 1.89 (s, 3H), 2.16 (m, 1H), 2.56 (m, 6H), 2.92 (m, 4H), 3.31 (m, 1H), 3.55 (s, 3H), 3.65 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H), 3.79 (m, 1H), 4.44 (d[AB], J = 15.0 Hz, 1H), 4.71 (d[AB], J = 15.0 Hz, 1H), 4.74 (d[AB], J = 15.0 Hz, 1H), 4.81 (d[AB], J = 15.0 Hz, 1H), 5.44 (s, 1H), 5.63 (s, 1H), 6.53 (m, 4H), 6.72 (s, 1H), 6.86 (d[AB], J = 8.7 Hz, 2H), 7.19 (d[AB], J = 8.7 Hz, 2H); FAB HRMS, *m/z* 875.4597, M + H calcd for $C_{51}H_{62}N_4O_9$ 875.4595.

Amide 38. A total of 383 mg (0.64 mmol, 2.0 equiv) of **19a** was charged into a flask along with 105 mg (0.32 mmol, 1.0 equiv) of recrystallized amide **37**[13d] and 37 mg (0.032 mmol, 0.10 equiv) of $Pd(Ph_3P)_4$. A total of 1.3 mL of anhydrous 1,4-dioxane was added, and the resulting solution was degassed and placed under an atmosphere of argon. Anhydrous Et_3N (2.6 mL) was then added, and the solution was heated at 50 °C for 24 h. The solution was cooled to room temperature and then diluted with 10% NH_4Cl solution (50 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, 50% ethyl acetate/hexanes) to afford 188 mg (74%) of **38** as an orange solid: R_f 0.28 (silica gel, 40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.02 (s, 3H), 2.15 (s, 3H), 2.53−2.60 (m, 4H), 2.90−2.95 (m, 4H), 2.99−3.04 (m, 2H), 3.12−3.17 (m, 2H), 3.66 (s, 3H), 3.68 (s, 3H), 5.69 (br s, 1H), 5.84 (br s, 1H), 6.74 (s, 1H), 7.09−7.12 (m, 2H), 7.42−7.45 (m, 2H). Anal. Calcd for $C_{33}H_{35}N_3ClO_5ISe$: C, 49.86; H, 4.44; N, 5.29. Found: C, 49.96; H, 4.44; N, 5.20.

3-Methyl-2-vinylpent-2-en-4-yne Carboxamide (**40b**). A total of 500 mg (1.53 mmol, 1.0 equiv) of amide **37** was dissolved in a solution consisting of 20 mL of THF, 2 mL of H_2O, and 0.4 mL of HOAc. An aqueous solution of 30% H_2O_2 (1.74 mL, 15.30 mmol, 10 equiv) was added, and the resulting brown solution was stirred at room temperature for 50 min. During this period, the solution became yellow. It was poured into ~50 mL of a saturated $NaHCO_3$ solution, which was then extracted with Et_2O. The combined ether layers were washed with brine and dried over $MgSO_4$. The resulting oily residue was concentrated under reduced pressure to afford 204 mg (98%) of **22** as an unstable yellow oil. *Caution*: do not concentrate completely to dryness or the residue may decompose in an exothermic fashion. Alkyne amide **40b** is very labile to polymerization and must be used immediately without further purification: R_f 0.34 (silica gel, 40% acetone/hexanes); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.39 (s, 1H) 5.33 (d, J = 11 Hz, 1H), 5.44 (d, J = 17 Hz, 1H), 6.92 (dd, J = 11 Hz, 17 Hz, 1H).

Amide 41. Method A. A total of 176 mg (0.22 mmol) of amide **38** was dissolved in 9.0 mL of anhydrous CH_2Cl_2. The resulting solution was cooled to −78 °C, and a solution consisting of 46 mg (0.26 mmol, 1.20 equiv) of recrystallized *m*-CPBA in 5 mL of anhydrous CH_2Cl_2 was added in a dropwise fashion, followed by 2 × 1 mL CH_2Cl_2 rinses. The resulting solution was stirred at −78 °C under argon for 1.5 h. Et_3N (0.18 mL) was then added, and the solution was stirred an additional 0.5 h at −78 °C and then allowed to warm to room temperature over 1.5 h. The solution was diluted with H_2O and extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was adsorbed onto silica gel and chromatographed as quickly as possible (silica gel, 50−70% ethyl acetate/hexanes) to afford **41** as an orange solid in 70% yield. In later experiments, the crude was used without purification due to cyclization to **42b** on the column: R_f 0.39 (silica gel, 40% acetone/hexanes; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.54 (t, J = 7.5 Hz, 4H), 2.91 (t, J = 7.5 Hz, 4H), 3.64 (s, 3H), 3.67 (s, 3H), 5.37 (d, J = 11 Hz, 1H), 5.49 (d, J = 18 Hz, 1H), 5.78 (br S, 1H), 6.09 (br s, 1H), 6.72 (s, 1H), 7.00 (dd, J = 11 Hz, 18 Hz, 1H). Anal. Calcd for $C_{27}H_{30}N_3O_5I$: C, 53.74; H, 5.01; N, 6.97. Found: C, 53.67; H, 4.98; N, 6.88.

Method B. A total of 1.40 g (2.35 mmol, 1.4 equiv) of **19a** was charged into a flask along with 271 mg (0.23 mmol, 0.10 equiv) of $Pd(Ph_3P)_4$ and 330 mg (2.44 mmol, 1.0 equiv) of crude alkyne amide **40b**. (see above). Anhydrous 1,4-dioxane (5.0 mL) was added to give a red brown solution. The solution was degassed and placed under an atmosphere of argon, and 9.5 mL of anhydrous Et_3N was added. The solution was heated at 50 °C for 17 h, cooled to room temperature, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed very quickly (silica gel, 50−70% ethyl acetate/hexanes) to afford 212 mg (15%) of **41** as an orange solid, identical to that described above in method A.

Iminolactone 42b. A solution of 149 mg (0.25 mmol) of amide **41** in 16 mL of $CHCl_3$ was heated at reflux under nitrogen for 31 h. The solution was cooled to room temperature, concentrated under reduced pressure, and chromatographed (silica gel, 20% acetone/hexanes) to afford 47 mg (32%) of **42b** as an unstable purple solid: R_f 0.73 (silica gel, 40% acetone/hexanes); IR($CHCl_3$) cm^{-1} 1736, 1669, 1598; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.11 (s, 3H), 2.15 (s, 3H), 2.54 (t, J = 7.5 Hz, 4H), 2.93 (t, J = 7.5 Hz, 4H), 3.65 (s, 3H), 3.67 (s, 3H), 5.61 (dd, J = 2 Hz, 11 Hz, 1H), 5.73 (s, 1H), 6.45−6.67 (m, 2H), 6.73 (s, 1H). Anal. Calcd for $C_{27}H_{30}N_3O_5I$: C, 53.74; H, 5.01; N, 6.97. Found: C, 53.82; H, 5.00; N, 6.88.[18]

Iminolactone Lactone 43c. The following reaction was run under foil and in the dark. A total of 5 mg (0.0055 mmol, 0.10 equiv) of tris(dibenzylidineacetone) dipalladium and 5 mg (0.023 mmol, 0.40 equiv) of tri-2-furylphosphine were combined in 0.8 mL of anhydrous DMF. The solution was degassed and placed under argon. After the solution was stirred for 3−5 min at room temperature, 35 mg (0.058 mmol, 1.0 equiv) of iodopyrrole **42b** and 18 mg (0.12 mmol, 2.0 equiv) of alkyne amide **32a** were added to the flask in one portion, followed by 0.8 mL of anhydrous NEt_3. The resulting purple solution was heated to 50 °C and stirred for 18 h. After this time period, the mixture was allowed to cool to room temperature and was then diluted with 10 mL of saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by PTLC (analtech uniplate silica gel, GHLF, 1000 μm, 40% acetone/hexanes) to afford 23 mg (63%) of **43c** as a blue film: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.42 (m, 6H), 2.00

(m, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 2.45−2.65 (m, 5H), 2.80−2.92 (m, 4H), 3.26 (m, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 3.85 (d, J = 10 Hz, 1H), 3.97 (m, 1H), 5.46−5.54 (m, 2H), 6.06 (s, 1H), 6.15 (s, 1H), 6.23−6.57 (m, 2H), 9.63 (s, 1H), 11.59 (s, 1H); exact mass calcd for $C_{35}H_{42}N_3O_8$ 632.2972, found 632.2974.

Lactone 46. A total of 222 mg (0.37 mmol) of amide **41** was dissolved in 16 mL of $CHCl_3$ to give an orange solution. TsOH (recrystallized, 210 mg, 1.10 mmol, 3.0 equiv) was added, and the reaction mixture immediately became purple. The mixture was stirred under argon in the dark (under foil) for 17 h. The mixture was then diluted with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 until it was no longer purple in color. The combined organic extracts (purple solution) were dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed (silica gel, 20% acetone/hexanes) to afford 110 mg (50%) of **46** as a crystalline brown solid: R_f 0.73 (silical gel, 40% acetone/hexanes); IR($CHCl_3$) cm^{-1} 1764, 1735, 1604; ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.14 (s, 3H), 2.21 (s, 3H), 2.49−2.56 (m, 4H), 2.85−2.97 (m, 4H), 3.64 (s, 3H), 3.66 (s, 3H), 5.56 (d, J = 11 Hz), 5.99 (s, 1H), 6.34−6.58 (m, 2H), 6.70 (s, 1H). Anal. Calcd for $C_{27}H_{29}N_2O_6I$: C, 53.65; H, 4.84; N, 4.64. Found: C, 53.75; H, 4.82; N, 4.57.

***O*-Benzyl Bis-lactone 48**. The following reaction was run under foil and in the dark. A total of 102 mg (0.17 mmol, 1 equiv) of iodopyrrole **46** was charged into a flask along with 16 mg (0.017 mmol, 0.10 equiv) of tris(dibenzylidineacetone)-dipalladium and 16 mg (0.069 mmol, 0.40 equiv) of tri-2-furylphosphine. To this mixture was added 3.6 mL of anhydrous CH_3CN, and the solution was degassed and stirred under argon for 3−5 min to allow formation of the active catalyst. A solution of 125 mg (0.51 mmol. 3.0 equiv) of the alkyne acid **47**[13a] in 3 mL of anhydrous CH_3CN was added, followed by 3.6 mL of anhydrous Et_3N. The bright purple solution was stirred at 50 °C for 18 h. The reaction was allowed to cool to room temperature and then poured into brine (50 mL). The mixture was extracted with EtOAc until the aqueous layer was no longer purple. The combined organic extracts (purple solution) were dried over Na_2SO_4, concentrated under reduced pressure, and purified by PTLC (silica gel, GHLF, 1000 μm, 30% acetone/hexanes) to afford 57 mg (47%) of **48** as a purple-blue film: ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3H), 1.20 (d, J = 8 Hz, 3H), 2.00 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.45−2.58 (m, 4H), 2.85−3.00 (m, 5H), 3.63 (s, 3H), 3.67 (s, 3H), 3.95−4.30 (m, 4H), 5.53 (dd, J = 2 Hz, 11 Hz, 1H), 5.88 (s, 1H), 6.29−6.54 (m, 3H), 6.77 (s, 1H), 6.85−6.95 (m, 2H), 7.15−7.23 (m, 3H); exact mass calcd for $C_{42}H_{47}N_2O_9$ 723.3282, found 723.3280.

Tetrapyrrole 16. The following two-step reaction was run under foil and in the dark. A total of 26 mg (0.036 mmol) of bis-lactone **48** was dissolved in 3 mL of anhydrous THF. The purple solution was cooled to −78 °C, and NH_3 was condensed into the reaction flask using a dry ice/acetone condenser, resulting in a solution containing about 10 mL of liquid NH_3. At −78 °C, **48** is converted into mono-lactone **49** within minutes (TLC). The reaction was kept under argon and was allowed to warm to reflux temperature (−33 °C), where the temperature was maintained by continuously adding dry ice to the condenser. After 7 h at −33 °C, the solution had an orange tint, and TLC analysis (silica gel, 50% acetone/hexanes) showed a lower R_f orange intermediate, presumed to be a hemi-aminal. The dry ice condenser was removed, and argon was then passed through the solution to hasten evaporation of NH_3. The resulting film was dissolved in 3 mL of CH_2Cl_2, and 20 mg (0.11 mmol, 3 equiv) of recrystallized TsOH was added to catalyze dehydration. The mixture was stirred at room temperature. The solution slowly changed color, going from red-orange to purple to blue. After a total of 3.5 h, the mixture was diluted with ∼10 mL of saturated $NaHCO_3$ solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by PTLC (silica gel, GHLF, 1000 μm, 30% acetone/hexanes) to afford 10 mg (40%) of **16** as a blue film: ^1H NMR ($CDCl_3$) δ 1.20−1.40 (m, 6H), 1.93 (s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.50−2.59 (m, 4H), 2.85−3.00 (m, 4H), 3.11 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.99 (m, 1H), 4.13 (m, 1H), 4.56−4.71 (m, 2H), 5.44 (m, 1H), 5.69 (s, 1H), 6.11 (s, 1H), 6.28 (m, 1H), 6.56 (m, 1H), 6.69 (s, 1H), 7.30−7.40 (m, 5H); exact mass calcd for $C_{42}H_{49}N_4O_7$ 721.3601, found 721.3600.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **19a**, **27a**,**b**, **28**−**30**, **31a**,**b**, **33a**,**b**, **34b**, **36**−**38**, **40b**, **41**, **42b**, **43c**, **46**, **48,** and **16**; X-ray crystallographic data for **42b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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