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A NOVEL SYNTHESIS OF PYRROMETHENONES

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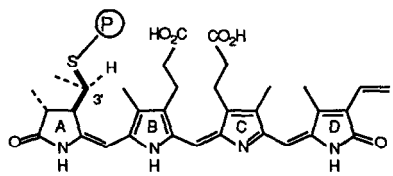
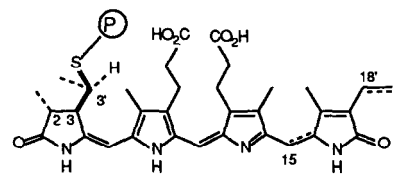
Summary: *Pyrromethenones are prepared by a process involving acylation of an N-aminopyrrole with a suitable acetylenic acid, followed by sequential 5-exo-dig cyclization and 3,5-sigmatropic shift.*

Phytochrome (**1a**) is a member of the biliprotein family of chromophores, which are made up of linear tetrapyrrole derivatives covalently bonded to a protein residue.[1] Together with the closely related species phycoerythrin (**1b**) and phycocyanin (**1c**), **1a** plays an active role in photomorphogenesis in higher plants.[2] This activity has been the subject of



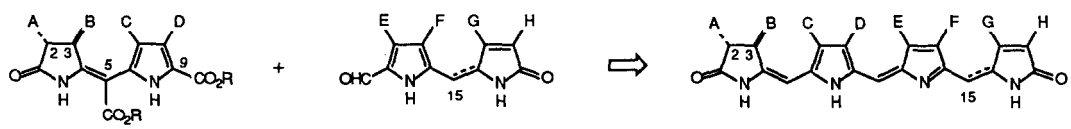
Phytochrome (1a)



1b; Δ-18'; **1c**; Δ-15

intensive study by plant physiologists for many years, and more recently, there has also been considerable effort directed toward the synthesis of model systems related to **1**.[1b] These latter studies are of importance if one is to better understand the photoreversible-photochromic behavior of **1a** associated with physiological activity.

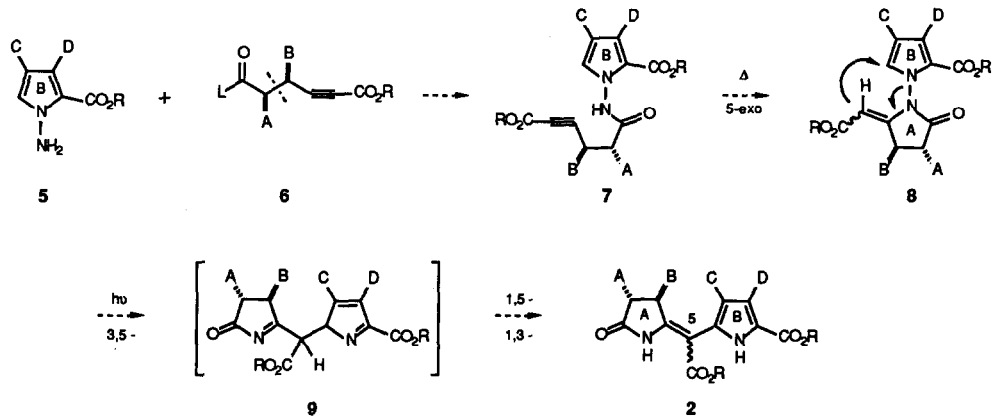
Synthetic methodology in this area should provide for the control of both relative and absolute stereochemistry (ring A), as well as regiochemical control along the backbone of the tetrapyrrole skeleton (substituents A-H, *cf.* **4**). In principle, this goal is readily attained by the decarboxylative coupling of two pyrromethenone units of general structure **2** and **3**, which is frequently a high yielding process.[3] In practice, however, pyrromethenones of type **2** are difficult to



2 **3** **4**

prepare with control over relative stereochemistry at C-2 and C-3,[4] and to the best of our knowledge, there have been no reports of enantiospecific syntheses. Regiochemical control is also frequently a problem with both **2** and **3**. These difficulties derive from the fact that the pyrromethenones themselves are invariably prepared by coupling of two pyrrole units, each of which must be selectively differentiated at positions 2 and 5.[3]

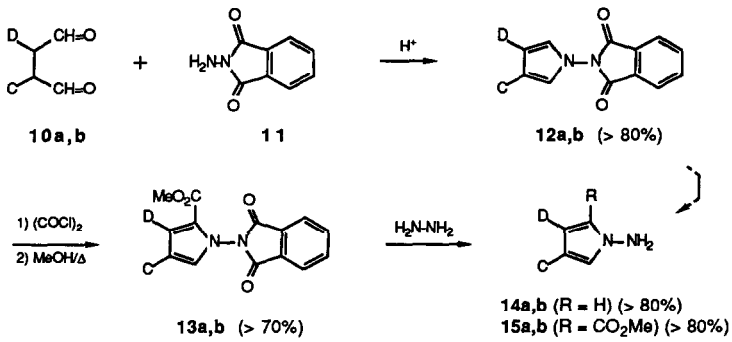
As an alternative strategy, we were interested in the possibility that pyrromethenones of general structure **2** might be derived from pyrrolohydrazides of type **7**, themselves prepared by acylation of 1-aminopyrroles **5** with a suitable carboxylic acid derivative **6** (Scheme 1). We envisioned that **7** might be converted by a *5-exo-dig* cyclization to the



Scheme 1

pyrrololactam **8**,[5] which upon 3,5-sigmatropic shift, and subsequent aromatization, would generate **2**.[6] In this way, stereochemical and regiochemical features incorporated into **6** could be transposed in an unequivocal fashion to the final product **2**.[7] A potential advantage of this approach resides in the fact that *syn*-substituted acetylenes of type **6** can now be prepared with excellent levels of diastereofacial selectivity using a modified Nicholas reaction (dashed line, **L** = chiral leaving group).[8] Thus, both relative and absolute stereochemistry in ring A would ultimately be controlled by well established principles of acyclic stereocontrol.

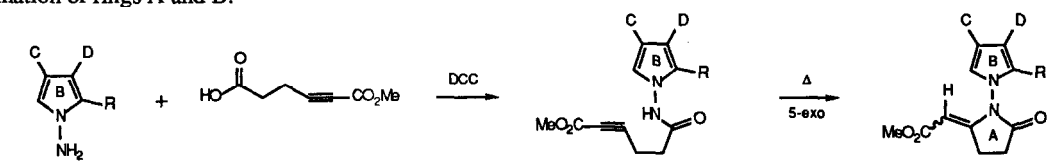
In this note, we describe model studies which demonstrate the feasibility of the transformation **7** --> **8** --> **2**. The key intermediates for these studies were the N-aminopyrroles **14a,b** and **15a,b**, which were readily derived from the appropriate dialdehyde precursors **10a,b** as indicated below (**a**: C,D = H; **b**: C,D = -[CH2]4-). Thus, condensation of



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

N-aminophthalimide (**11**) with **10a,b** gave an excellent yield of the protected N-aminopyrroles **12a,b**,[9] which could be directly cleaved to the aminopyrroles **14a,b** with hydrazine in ethanol, or converted to the methyl esters **13a,b** with oxaloyl chloride/$AlCl_3$ followed by methanolysis.[10] Hydrazinolysis of **13a,b** then proceeded routinely to afford the aminoesters **15a,b** with no complications due to ester aminolysis.[11]

Once in hand, both **14a,b** and **15a,b** were cleanly coupled with the acetylenic acid **16** to provide the hydrazide derivatives **17a,b** and **18a,b**. These latter materials then underwent a facile 5-*exo-dig* cyclization to afford either **19a,b** or **20a,b** in > 90% yield (~ 3 : 1 mixture of E- and Z-isomers; **a**: C,D = H; **b**: C,D = -[CH_2]$_4$-). This step completed the formation of rings A and B.



14a,b (R = H)
15a,b (R = CO_2Me)

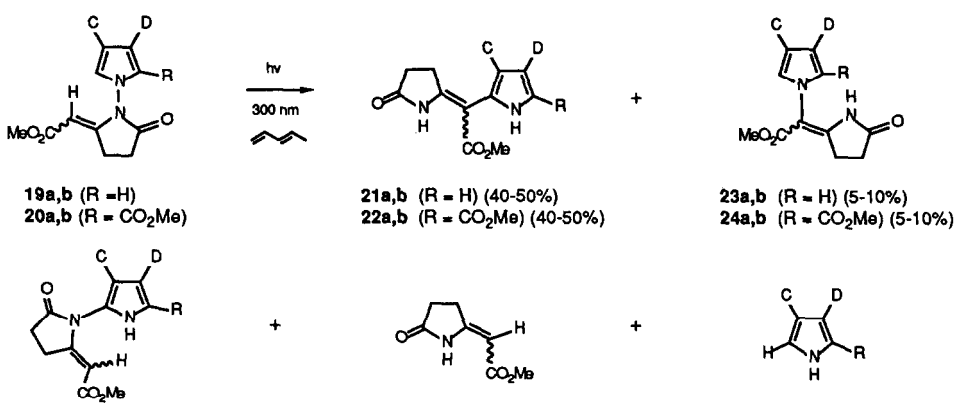
16

17a,b (R = H) (70-80%)
18a,b (R = CO_2Me) (60-70%)

19a,b (R = H) (> 90%)
20a,b (R = CO_2Me) (> 90%)

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

Numerous conditions were examined for the conversion of **19a,b** and **20a,b** to the isomeric pyrromethenones **21a,b** and **22a,b** (Scheme 2). These materials were stable to thermolysis at temperatures up to 250° C, and at higher temperatures suffered only slow decomposition to intractable materials. All attempts at acid catalysis were unproductive. However, upon photolysis, **19a,b** and **20a,b** gave reaction mixtures which contained the desired products of 3,5-sigmatropic shift (**21,22**), as well as products corresponding to 1,3- and 1,5-sigmatropic shifts (**23-26**), and N-N bond cleavage (**27-29**). The ratio of products **21** - **29** was strongly dependent upon the presence or absence of triplet state quenchers. For example, at 300 nm **19a** (E- or Z-isomer) gave 10-15% yields of the rearrangement products **21a**, **23a** and **25a**, together with a larger proportion of the cleavage products **27** and **28a**. Similar results were obtained at 253 nm. *In the presence of piperylene (triplet quencher),*[12] *however, cleavage was reduced to trace amounts and* ***21a*** *was*



19a,b (R = H)
20a,b (R = CO_2Me)

21a,b (R = H) (40-50%)
22a,b (R = CO_2Me) (40-50%)

23a,b (R = H) (5-10%)
24a,b (R = CO_2Me) (5-10%)

25a,b (R = H) (15-20%)
26a,b (R = CO_2Me) (15-20%)

27 (0-5%)

28a,b (R = H) (0-5%)
29a,b (R = CO_2Me) (0-5%)

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

Scheme 2

obtained in 40-50% yield as an equilibrium mixture of E- and Z-isomers (~ 1 : 1).[7] Similar results were obtained with **19b**, and in identical fashion, **20a,b** gave a 40-50% yield of the target pyrromethenones **22a,b**. The structure of **22b** (E-isomer) was unequivocally established by single crystal X-ray analysis.[13]

The results summarized in Scheme 2 are consistent with a reaction pathway in which photodissociation occurs *via* a triplet state, in competition with a singlet state 3,5-sigmatropic shift. In the presence of triplet sensitizers the cleavage products **27-29** were the only products observed. Further mechanistic studies of this reaction are in progress, and the applicability of this methodology for the synthesis of homochiral pyrromethenones will be the subject of a future report.[14]

References and Notes

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4. See, for example, Schoenleber, R.W.; Kim, Y.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 2645.
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11. Satisfactory analytical and spectral data were obtained for all new compounds reported. Physical and chemical data for representative compounds: (a) **18b:** colorless crystalline solid, mp 115-16° C, Rf 0.2 (70:30 hexanes/EtOAc, silica gel); mass spectrum, m/e 332 (M+); IR(KBr) 3272, 2238, 1729, 1701, 1681 cm^{-1}; NMR($CDCl_3$) δ 1.60 (m, 4H), 2.39 (m, 2H), 2.51-2.69 (m, 6H), 3.63 (s, 3H), 3.65 (s, 3H), 6.60 (s, 1H), 8.56 (br s, 1H). **Anal.** Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 61.45; H, 6.10; N, 8.38. (b) **20b** (Z-isomer): colorless crystalline solid, mp 112-13° C, Rf 0.7 (70:15:15 CH_2Cl_2/EtOAc/hexanes, silica gel); mass spectrum, m/e 332 (M+); IR($CHCl_3$) 3019, 1765, 1702, 1688 cm^{-1}; NMR($CDCl_3$) δ 1.69 (m, 4H), 2.52 (m, 2H), 2.66 (m, 1H), 2.72 (m, 1H), 2.75 (m, 2H), 2.86 (m, 1H), 3.01 (m, 1H), 3.28 (s, 3H), 3.72 (s, 3H), 5.03 (s, 1H), 6.59 (s, 1H). **Anal.** Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 61.50; H, 6.12; N, 8.39. (c) **20b** (E-isomer): colorless crystalline solid, mp 107-8° C, Rf 0.8 (70:15:15 CH_2Cl_2/EtOAc/hexanes, silica gel); mass spectrum, m/e 332 (M+); IR($CHCl_3$) 3032, 1762, 1702, 1648 cm^{-1}; NMR($CDCl_3$) δ 1.72 (m, 4H), 2.51 (m, 2H), 2.68 (m, 1H), 2.77 (m, 2H), 2.80 (m, 1H), 3.26 (m, 1H), 3.45 (m, 1H), 3.64 (s, 3H), 3.71 (s, 3H), 4.73 (t, 1H, J = 2.5 Hz), 6.50 (s, 1H). (d) **22b** (E-isomer): colorless crystalline solid, mp 214-15° C, Rf 0.3 (70:15:15 CH_2Cl_2/EtOAc/hexanes, silica gel); mass spectrum, m/e 332 (M+); IR($CHCl_3$) 3452, 3386, 3025, 2936, 2858, 1755, 1698, 1621 cm^{-1}; NMR($CDCl_3$) δ 1.71 (m, 4H), 2.22 (t, 2H, J = 6.0 Hz), 2.62 (m, 2H), 2.78 (t, 2H, J = 6.0 Hz), 3.39 (m, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 7.40 (br s, 1H), 8.75 (br s, 1H). **Anal.** Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 61.14; H, 6.12; N, 8.37. Structure confirmed by X-ray analysis.[13]
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13. We are grateful to Ms. Gayle Schulte, of Yale University, for performing the X-ray analysis on **22b** (E-isomer).

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