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A Conceptually New Approach to the Synthesis of Linear Tetrapyrroles Related to Phytochrome

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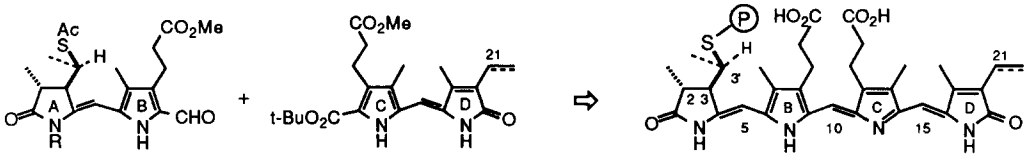
Abstract: Linear tetrapyrroles **9**, of a type related to phytochrome (**3**), have been prepared by TBAF catalyzed 5-*exo*-*dig* cyclization of *bis*-acetylenic amides **8**.

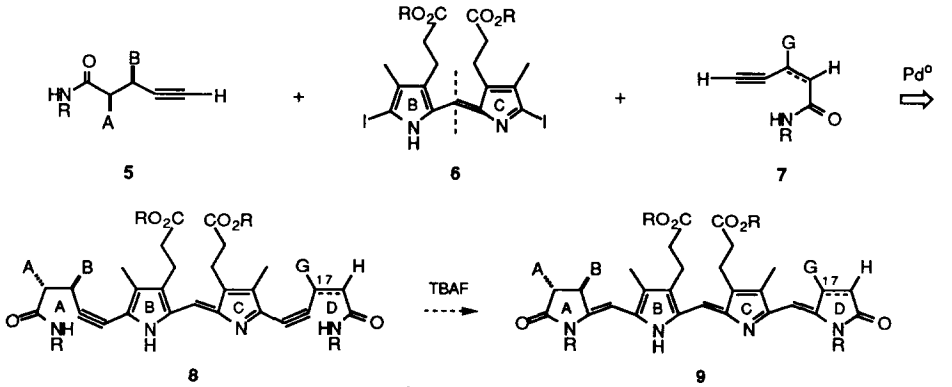
In previous papers in this area we described efficient syntheses of pyrromethenones of general structure **1b-2**,[1] which are attractive precursors for the preparation of biologically important tetrapyrroles such as phytochrome (**3**), phycocyanin (**4**) and related compounds (P = protein).[2] In principle, linear tetrapyrroles of type **3**,**4**



1a,b (R = H; PMB) **2a** (Δ-21); **2b** (sat'd -21) **3** (Δ-21); **4** (sat'd -21)

can be derived by acid catalyzed condensation of **1** and **2**, taking advantage of the ease of decarboxylation of *t*-butylesters of type **2** for forming the methine bridge at C_{10}.[3] This approach follows the classical AB + CD --> ABCD strategy employed in most syntheses of model compounds of this class.[2b,3]

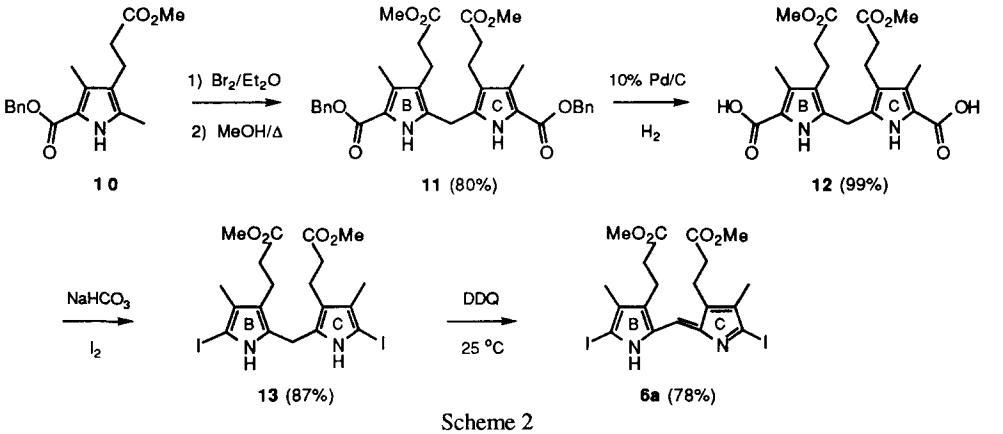
As an alternative approach to **3**,**4**, we have been interested in the possibility that acetylenic amides of general structure **8** might undergo facile cyclization to linear tetrapyrroles **9** upon TBAF catalysis (Scheme 1). As in the case with **1b-2**,[1] this strategy would make use of a Nicholas-Schreiber reaction for preparing rings A and D in homochiral form (**5**), and with unambiguous control over regiochemistry (**5** and **7**).[1,4] However, the starting point in this approach is the ring-B,C fragment **6**, which takes advantage of the natural symmetry associated with rings B and C in linear tetrapyrroles of type **9** (BC + D + A --> ABCD).[5] In addition, this strategy would allow for incorporation of the most sensitive portion of the molecule (ring A) at a later stage of the synthesis.



5 **6** **7** **8** **9**

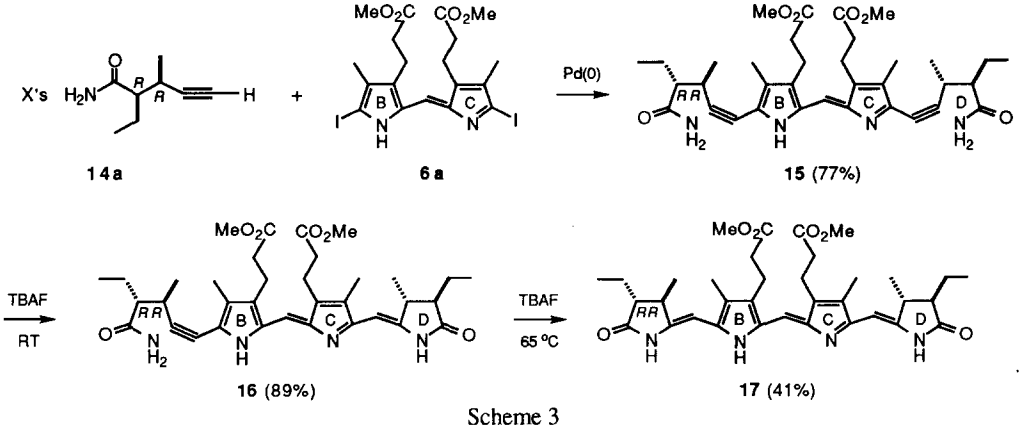
Scheme 1

In order to explore this route, we have developed a highly efficient synthesis of bis-iodo derivative **6a**, which can be carried out on multigram scales beginning with the readily available pyrroloester **10** (Scheme 2).[6] Following literature precedent,[7a] bromination of **10** in Et_2O, followed by brief heating in MeOH, afforded an 80% yield of dipyrrole **11** with no need for isolation of intermediates. This last material was then converted to the known bis-iodo dipyrrole **13** in 86% overall yield by a two step sequence involving catalytic hydrogenation to give the free bis-dicarboxylic acid **12** (99%),[7b] followed by decarboxylative iodination (87%).[7c] Finally, oxidation of **13** with DDQ gave a 78% yield of the desired ring-B,C fragment **6a** as a stable, crystalline compound (mp 139-40 °C).[5,7d,9]



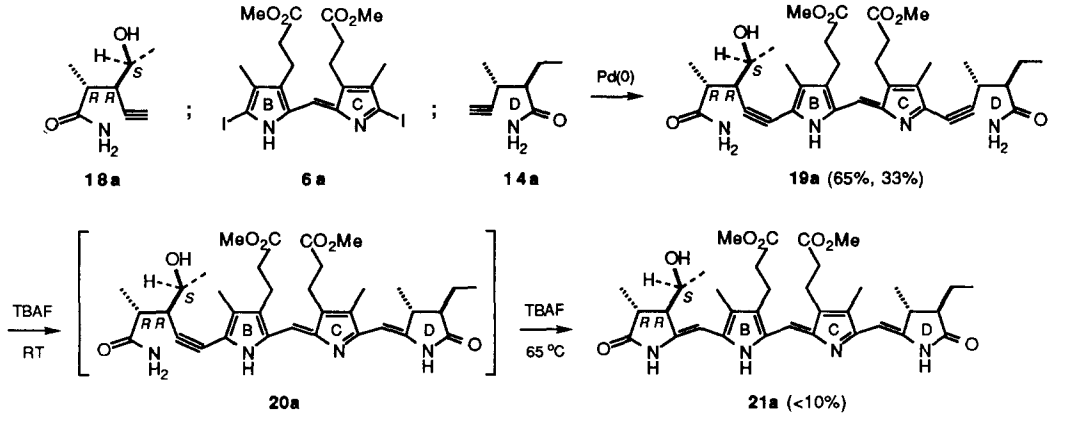
Scheme 2

Our initial cyclization experiments were carried out with the symmetrical bis-acetylenic amide **15**, which was prepared in 77% yield by Pd(0) mediated coupling of bis-iodo derivative **6a** with excess homochiral acetylenic amide **14a** (Scheme 3).[1b,c] As expected, **15** underwent a facile 5-*exo*-*dig* cyclization upon catalysis with $Bu_4N^+F^-$ (TBAF),[1b] affording an 89% yield of mono-cyclized intermediate **16** after 1.5 h at 25 °C (*Z*-stereochemistry only; note that rings A and D are equivalent). Interestingly, however, cyclization of **16** to **17** was considerably slower, requiring 5 h at 65 °C for complete reaction (4 eq TBAF). In this case, we believe, cyclization of ring A is inhibited by the electron donating ability of the ring D enamide functionality (*cf.* **16**), a point which will be discussed further below. In any event, we were sufficiently encouraged by these results to apply this same approach to unsymmetrical tetrapyrroles.



Scheme 3

Following an analogous procedure, unsymmetrical bis-acetylenic amide **19a** was prepared by sequential coupling of **6a** first with ring D precursor **14a** (65%), followed by the less stable ring A precursor **18a** (Scheme 4).[1e,5] As described above (Scheme 3), mono-cyclization involving ring D was once again fast, affording **20a** after 1.5 h at 25 °C. In this case, however, cyclization of ring A was very slow, affording only trace amounts of the desired tetrapyrrole **21a** after 7 h at 65 °C (6 eq TBAF). This reaction was also accompanied by substantial decomposition.

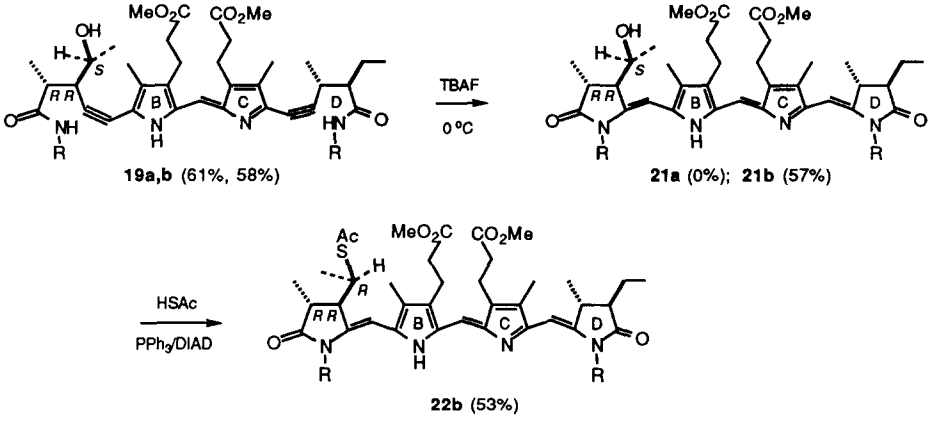


18a ; **6a** ; **14a** → **19a** (65%, 33%)

20a → **21a** (<10%)

Scheme 4

Much more satisfactory results were obtained with the bis-acetylenic amide **19b** (R = *p*-methoxybenzyl; Scheme 5), which was prepared in good overall yield by sequential Pd(0) mediated coupling of **6a** with the corresponding *p*-methoxybenzyl amides **14b** and **18b**.[5] As we have previously described, N-substitution can have a dramatic effect on the rate of acetylenic amide cyclization.[1d,e] *This turned out to be especially true for* ***19b****, which gave a 57% yield of tetrapyrrole* ***21b*** *after 1.5 h at 0 °C.* By way of comparison, **19a** (R = H) was completely unreactive to these conditions, even after extended reaction periods. In addition, we were pleased to find that thia-Mitsunobu inversion at C_3' occurred in routine fashion,[8] affording a 53% yield of tetrapyrrole **22b** having the desired 2*R*,3*R*,3'*R*-configuration found in **3**,**4**.[2] Neither of these reactions has been optimized.



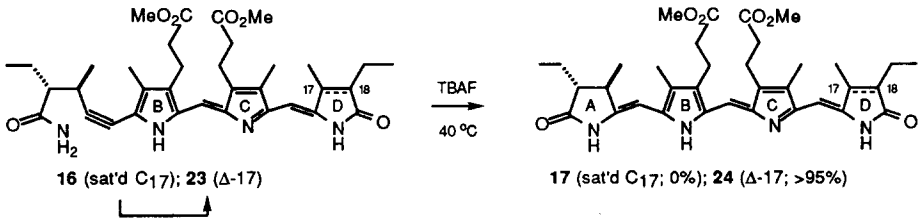
19a,b (61%, 58%) → **21a** (0%); **21b** (57%)

22b (53%)

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

Scheme 5

Finally, it was of interest to explore the effect of ring D oxidation state on the rate of cyclization leading to ring A. These studies were carried out with acetylenic amides **16** and **23**, which differ only in oxidation state at C_{17}-C_{18} (Scheme 6; **23** was prepared by DDQ oxidation of **16**).[1c] One would expect that cyclizations involving **23** (Δ-17) would be accelerated, since the acetylenic amide in **23** (but not in **16**) 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, **16** (sat'd C_{17}) was completely unreactive toward cyclization to **17** with TBAF at 40 °C. Under identical conditions, however, **23** (Δ-17) gave an essentially quantitative yield of tetrapyrrole **24** (Δ-17) having the natural oxidation state. Based upon these results, we expect that cyclizations of type **8** --> **9** (Δ-17) will be particularly facile (*cf.* Scheme 1). Application of this methodology to the synthesis of phytochrome (**3**) and related compounds is currently under investigation.[9,10]



Scheme 6

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5. Both **6** and **6a** have a pseudo plane of symmetry, since the pyrrole rings freely interconvert *via* tautomerization (upon protonation, rings B and C are equivalent, as determined by NMR studies on **6a** at low pH). Therefore, for the purpose of regiochemical control, it makes little difference which acetylenic fragment is coupled first. However, for stability reasons it is desirable to add the least stable ring A-synthons **18** last.
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9. Satisfactory spectral data was obtained for all new compounds reported. **21b**: ^{1}HNMR (300 MHz, $CDCl_3$): 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); -OH and -NH not observed. Copies of NMR spectra will be provided upon request.

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