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An Unequivocal Synthesis of the Ring-A,B Dihydropyrromethenone of Phytochrome

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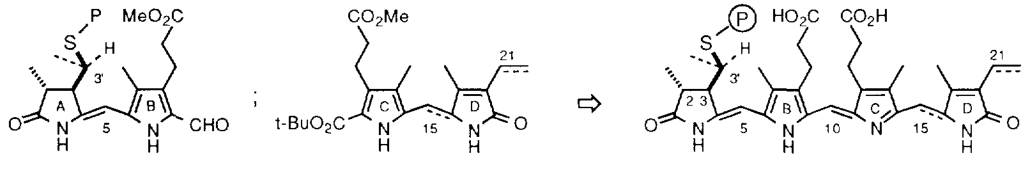
Abstract: Dihydropyrromethenone **1b** (R = *p*-methoxybenzyl), a potential precursor for the synthesis of phytochrome (**3**), has been prepared in enantiomerically pure form beginning with the homochiral acetylenic lactone **18**.

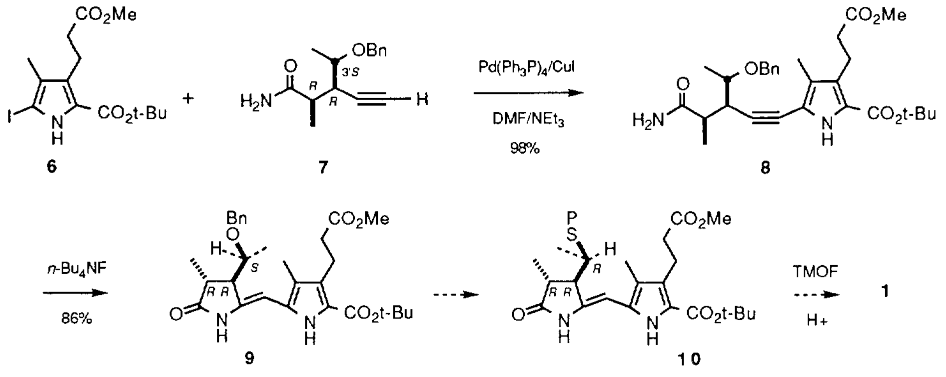
The biliproteins are a family of naturally occurring chromophores which are made up of linear tetrapyrrole derivatives covalently bonded to a protein (P). Representative examples include phytochrome (**3**), which functions as the "on-off" switch for photomorphogenesis in higher plants,[1] and the phycocyanins (**4**) and phycoerythrins (**5**).[1h-j] These last materials are commonly found in blue-green, eucaryotic and cryptomonad algae and serve as light harvesting proteins in photosynthesis. Phytochrome (**3**) has been implicated in such light-dependent, irreversible processes as seed germination, flowering, and stem and leaf growth.[1a]



1 **2a** (Δ-15, Δ-21); **2b** (Δ-15); **2c** (Δ-21) **3** (Δ-15, Δ-21); **4** (Δ-15); **5** (Δ-21)

In principle, linear tetrapyrroles of type **3-5** can be synthesized by acid catalyzed condensation of the appropriate pyrromethenones **1** and **2**, taking advantage of the ease of decarboxylation of *t*-butylesters of type **2** for forming the methine bridge at C_{10} (see above).[2] In an earlier paper we described efficient syntheses of pyrromethenones **2a** and **2b**, the ring-C,D precursors to **3** and **4**.[3c] In this note we report the first enantiospecific synthesis of ring-A,B dihydropyrromethenones of type **1**.

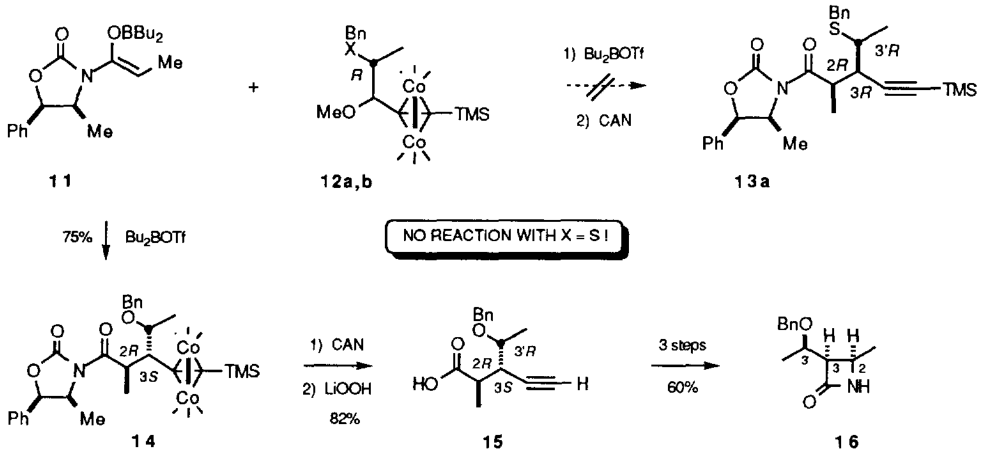
We initially planned that 3'*R*-dihydropyrromethenones of type **10** might be derived via thia-Mitsunobu inversion of the 3'*S*-benzyloxy derivative **9** (Scheme 1),[4] itself derived in excellent overall yield from iodopyrrole



Scheme 1

6 and homochiral acetylenic amide **7**.[3b] Decarboxylative formylation of **10** with trimethylorthoformate (TMOF) would then afford the desired ring-A,B precursor **1**.[2] However, this approach turned out to be impractical, since **9** suffered extensive decomposition upon attempted benzyl ether cleavage (H_2/Pd, BBr_3, Me_3SiI, etc.).

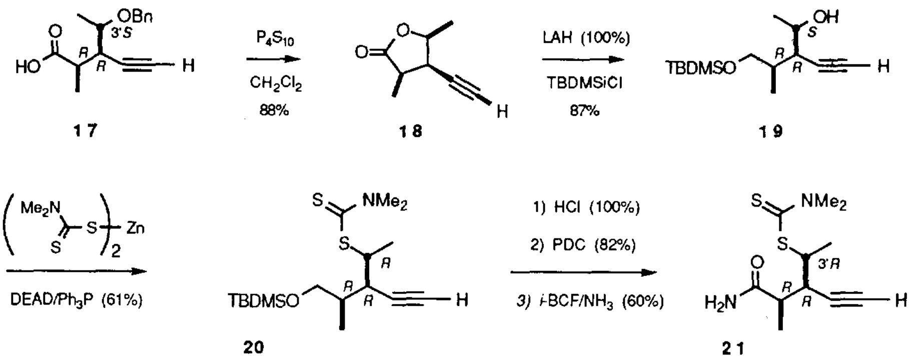
We also explored the possibility that 3'*R*-benzyl mercaptide derivatives of type **13a** could be prepared using a Nicholas-Schreiber reaction (Scheme 2),[5] as previously employed for the synthesis of the 3'*S*-benzyl ether **7**.[3] Surprisingly, however, all attempts at the direct condensation of boron enolate **11** with *R*-cobalt complex **12a** (X=S) were unsuccessful. At low temperatures little or no reaction was observed, while more forcing conditions caused rapid decomposition. This reaction was also problematic with the *R*-benzyl ether **12b** (X=O), which reacted in a mis-matched fashion with **11** to afford *anti*-adduct **14** in 75% yield (12:1 selectivity).[6] The structure of **14** was unequivocally proven by a three step sequence involving Curtius rearrangement, followed by oxidative cleavage and DCC catalyzed cyclization to afford the known ß-lactam derivative **16** (60% overall yield).[6] We believe this to be the only reported example of a Nicholas-Schreiber condensation proceeding with *anti*-selectivity, and it serves to illustrate the powerful directing influence of the chiral substituent in **12b**.



a: X = S; **b**: X = O

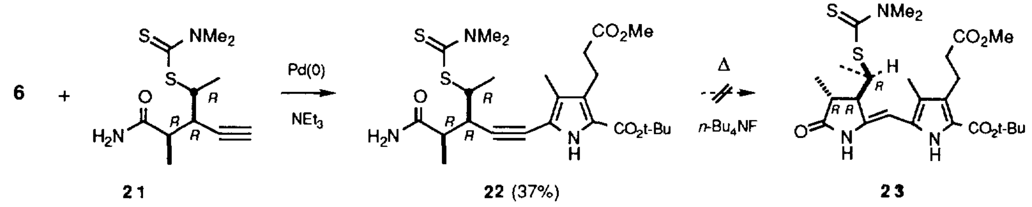
Scheme 2

These difficulties were partially circumvented with our finding that the 3'*R*-mercaptide derivative **21** could be obtained from the 3'*S*-benzyl ether **17** by the route outlined in Scheme 3. Thus, debenzylation of **17** with



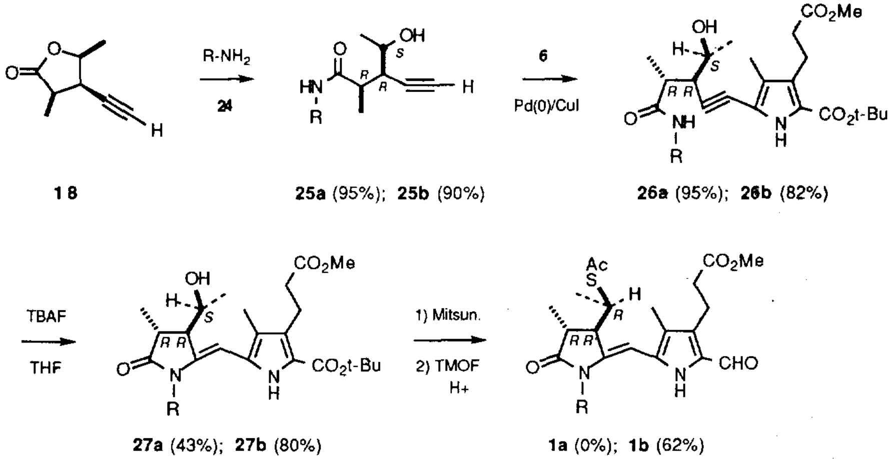
Scheme 3

P_4S_{10} led directly to the lactone derivative **18** (88%),[7] which upon LAH reduction and selective protection (TBDMSiCl) gave an 87% yield of the secondary alcohol **19**. This last material then underwent clean thia-Mitsunobu inversion with the reagent system ZIRAM/DEAD/Ph_3P,[8] affording a 61% yield of the desired 2*R*,3*R*,3'*R* mercaptide **20**. Once in hand, **20** was converted in 49% overall yield to the acetylenic amide **21** by a three step sequence involving deprotection, followed by oxidation, and finally amidation with *i*-butylchloroformate (*i*-BCF) and NH_3. Although circuitous, this route could be utilized to prepare gram quantities of **21** with excellent stereocontrol. Unfortunately, however, **21** gave only modest yields of acetylenic pyrrole **22** upon Pd(0) catalyzed coupling with iodopyrrole **6** (Scheme 4; cf. also Scheme 1).[9] Furthermore, all attempts at the TBAF-catalyzed cyclization of **22** to the desired dihydropyrromethenone **23** led to extensive decomposition.[3b]



Scheme 4

On the basis of these results, we concluded that the 3'*R*-mercaptide functionality would best be introduced <u>after</u> formation of the dihydropyrromethenone ring. This was accomplished as diagrammed in Scheme 5. As the key step in this sequence, lactone **18** underwent a facile ring opening with a variety of amines **24** to afford acetylenic amides of type **25** in 90-95% yield. Acetylenic amides **25a,b** (R=H, PMB) then gave 80-95% yields of the corresponding pyrroloacetylenes **26a,b** upon Pd(0) catalyzed coupling with iodopyrrole **6**.[9] In preliminary studies, 5-*exo-dig* cyclization of **26a** was very slow, affording a 43% yield of **27a** after 48 h at reflux with 6 eq of TBAF (Scheme 5). Moreover, all attempts at the thia-Mitsunobu inversion of **27a**,[4] followed by decarboxylative formylation,[2] were unsuccessful. This last result is at least partly due to the unstable nature of **27a** (R=H). In contrast to the case with R=H, however, cyclizations of type **26** --> **27** were dramatically



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

Scheme 5

accelerated by N-substitution, which also imparts an added degree of stability (see also preceeding paper).[10] Of particular interest, **26b** (R = *p*-methoxybenzyl) afforded an 80% yield of 3'*S*-hydroxydihydropyrromethenone **27b** upon brief warming with 1 eq of TBAF (*Z*-isomer exclusively). This result is in marked contrast to that obtained with **26a** (R=H), which afforded <10% of **27a** under identical conditions. Finally, we were pleased to find that **27b** gave a 62% overall yield of the desired ring-A,B precursor **1b** (R=PMB) upon thia-Mitsunobu inversion,[4] followed by acid catalyzed decarboxylative formylation.[2] Since the *p*-methoxybenzyl group can be removed under a variety of mild conditions,[11] **1b** represents a convenient ring-A,B synthon for eventual elaboration to phytochrome (**3**).[12,13] The results of these last experiments will be reported in the near future.

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12. NMR data for compound **27b**: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.19 (d, J = 6.00 Hz, 3H), 1.39 (d, J = 7.20 Hz, 3H), 1.60 (s, 9H), 1.83 (s, 3H), 2.55 (m, 2H), 2.61 (t, J = 8.40 Hz, 2H), 3.04 (t, J = 8.40 Hz, 2H), 3.69 (s, 3H), 3.76 (s, 3H), 4.21 (d, J = 15.00 Hz, 1H), 4.77 (d, J = 15.00 Hz, 1H), 5.33 (s, 1H), 6.55 (d, J = 8.70 Hz, 2H), 6.69 (d, J = 8.70 Hz, 2H), 8.21 (br, 1H). NMR data for compound **1b**: ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.25 (d, J = 7.20 Hz, 3H), 1.37 (d, J = 7.50 Hz, 3H), 1.82 (s, 3H), 2.09 (s, 3H), 2.52 (m, 1H), 2.58 (t, J = 8.10 Hz, 2H), 3.02 (t, J = 8.10 Hz, 2H), 3.61 (m, 1H), 3.67 (s, 3H), 3.79 (s, 3H), 4.49 (d, J = 15.00 Hz, 1H), 4.89 (d, J = 15.00 Hz, 1H), 5.55 (s, 1H), 6.85 (d, J = 8.70 Hz, 2H), 7.22 (d, J = 8.70 Hz, 2H), 9.13 (br, 1H), 9.56 (s, 1H). Copies of NMR spectra will be provided upon request.
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