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Tetrapyrroles. III. Homochiral Dihydropyrromethenones From N-Aminopyrroles and Acetylenic Acids

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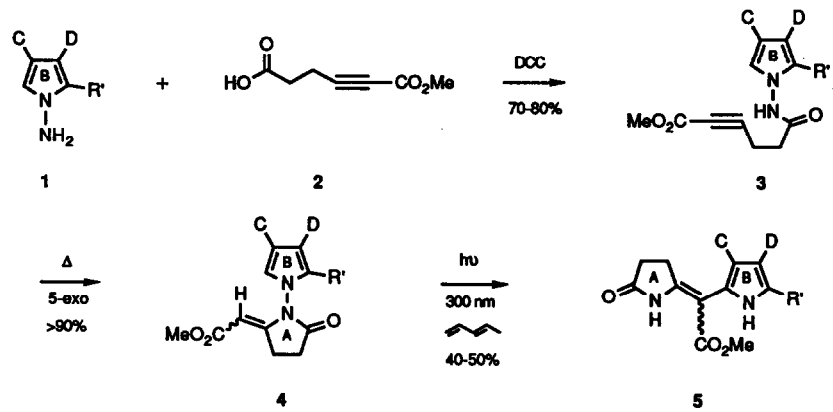
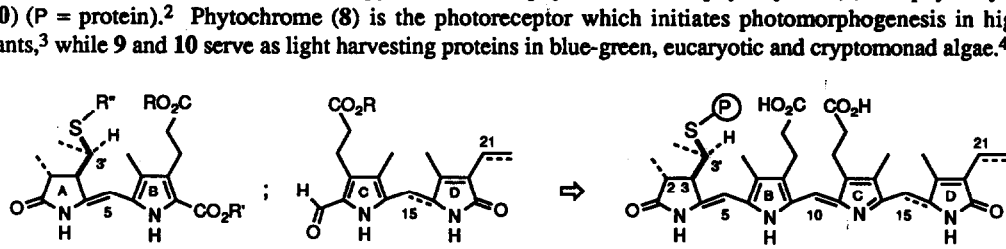
Abstract: *Dihydropyrromethenone 29, a potential precursor for the synthesis of Phytochrome (8), Phycocyanin (9) and Phycoerythrin (10), has been prepared in homochiral form from pyrrolohydrazide 27 by a sequence involving F· induced 5-exo-dig cyclization to afford enamide 28, followed by photochemical 3,5-sigmatropic rearrangement.*

We have recently reported that pyrrolohydrazides of general structure **3** (C,D = H, -[CH$_2$]$_4$- ; R' = H, CO$_2$Me) undergo a facile 5-*exo-dig* cyclization, affording enamides of type **4** which can be converted in good yield to dihydropyrromethenones **5** by photochemical 3,5-sigmatropic rearrangement.[1] These transformations are of

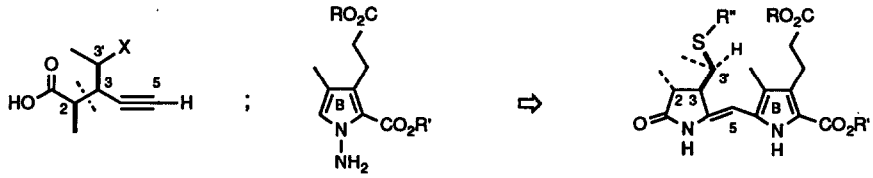


Scheme 1

interest since **5** is closely related to ring-A,B fragments of type **6**, which are attractive precursors for the synthesis of biologically important linear tetrapyrroles such as phytochrome (**8**), phycocyanin (**9**) and phycoerythrin (**10**) (P = protein).[2] Phytochrome (**8**) is the photoreceptor which initiates photomorphogenesis in higher plants,[3] while **9** and **10** serve as light harvesting proteins in blue-green, eucaryotic and cryptomonad algae.[4]



Pyrrolohydrazides **3** are most conveniently prepared by carbodiimide coupling of acetylenic acid **2** with N-aminopyrroles of type **1**,[1] which in our original studies were limited to symmetrical ring systems due to the difficulty of preparing derivatives where C ≠ D. However, in principle the strategy outlined in Scheme 1 could be employed in the synthesis of species such as **8-10** with unequivocal control over both relative and absolute stereochemistry (ring A), as well as regiochemical control along the backbone of the tetrapyrrole skeleton (rings A - D). The viability of this approach depends mainly upon the availability of unsymmetrical N-aminopyrroles of type **11** and properly substituted acetylenic acids of type **12**. In a previous paper in this series we described

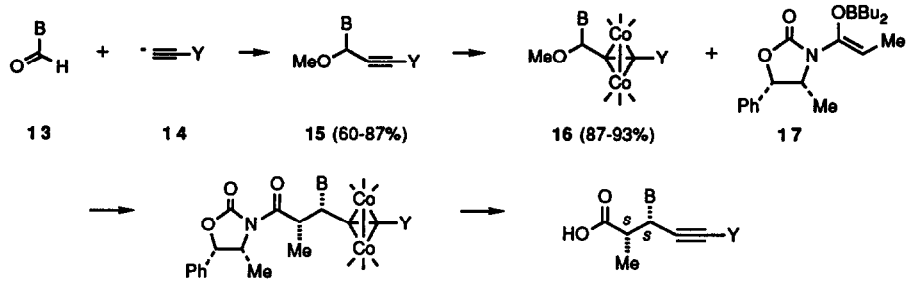


12 **11** **6**

R = Me, Et, TMS, TBDMS, TIPS; **R'** = Et, Bn

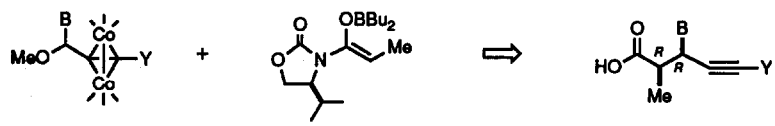
a novel synthesis of **11** which is completely unambiguous and accomodates a diverse range of substitution patterns.[5] In this note we describe the preparation of acetylenic acids of type **12**, and enantiomeric species, and their utility in the synthesis of homochiral dihydropyrromethenones having the substitution pattern found in **6**.

In 1987, Schreiber *et al.* considerably increased the scope of the Nicholas reaction with their finding that alkylations can be carried out with both excellent diastereo- *and* enantioselectivity with homochiral nucleophiles.[6] As one example, reaction of Evans' enolate **17** with the cobalt complex **16b** (**B** = Me, **Y** = TMS) afforded an 80% yield of adduct **18b** (**B** = Me, **Y** = TMS) as a 12:1 mixture of *syn*- and *anti*-isomers (Scheme 2). We have expanded upon this methodology to prepare a wide variety of Nicholas adducts **18**, many of which were converted to the corresponding 2*S*,3*S*-acetylenic acids **19** by oxidative decomplexation and hydrolysis



13 **14** **15** (60-87%) **16** (87-93%) **17**

18 (90-98%) **19** (60-88%)



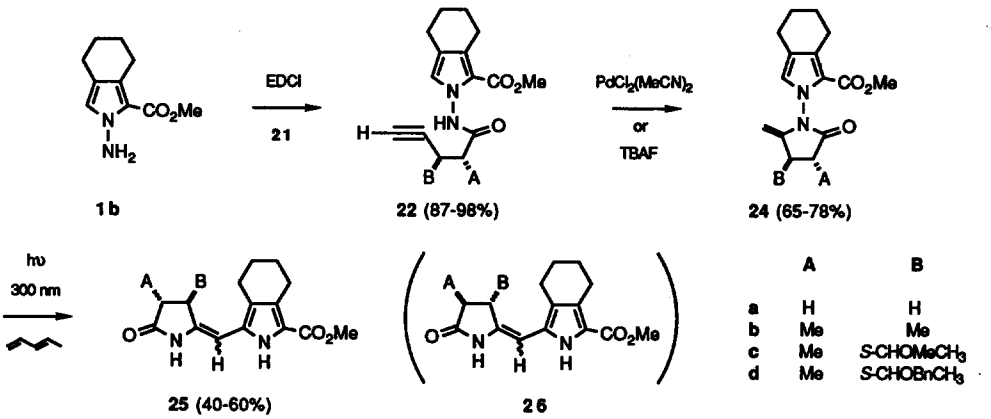
16 (87-93%) **20** **21** (85-87%)

Y = CO_2Bn, $CO_2CMe_2CCl_3$, CO_2H, TMS, TBDMS, H; **B** = Me, *S*- and *R*-CHOMeCH$_3$, *S*- and *R*-CHOBnCH$_3$

Scheme 2

(Y = H, CO_2H, TMS, TBDMS; B = Me, *S*- and *R*-CHOBnCH$_3$).[6,7] In analogous fashion, but using oxazolidinone **20**, 2*R*,3*R*-acetylenic acids **21** (Y = H) were obtained in excellent chemical yield and with *syn*-selectivity on the order of 12:1 to >50:1 (In general, selectivity increases with increasing size of Y, as previously noted by Schreiber[6]). Of particular interest, homochiral acetylenic acids **21c,d** (**c**: B = *S*-CHOMeCH$_3$, Y = H; **d**: B = *S*-CHOBnCH$_3$, Y = H) were prepared in 38% (**21c**) and 68% (**21d**) overall yield from aldehydes **13c,d** (**c**: B = *S*-CHOMeCH$_3$; **d**: B = *S*-CHOBnCH$_3$)[8] with >98% *syn*-selectivity. Both **21c** and **21d**, the latter of whose structure was unequivocally proven by X-ray analysis,[9a,b] contain all of the stereochemical features necessary for incorporation into **6**.

The utility of these acetylenic acids for the synthesis of homochiral dihydropyrromethenones was first explored with model pyrrolohydrazides of type **22a-d** (A = H, Me; B = H, Me, *S*-CHOMeCH$_3$ and *S*-CHOBnCH$_3$), which were readily prepared by coupling of acids **21a-d** with N-aminopyrrole **1b** (C,D = -[CH$_2$]$_4$- ; R' = CO_2Me) (Scheme 3).[1] We experienced considerable difficulty in our initial attempts at carrying out *5-exo-dig*



Scheme 3

cyclizations of **22** to **24**, which in contrast to **3** require nucleophilic addition to unactivated acetylenes (*cf.* Scheme 1).[1] Not surprisingly, hydrazides **22** resisted all attempts at cyclization under thermal conditions, and were unreactive or slowly decomposed under conditions of acid or base catalysis. Eventually, some measure of success was achieved with the reagent system PdCl$_2$(MeCN)$_2$,[10] which afforded ~70% yields of enamides **24** together with unidentified polar products. However, we found that by far the best procedure involved warming **22** with excess *n*-Bu$_4$NF in THF,[11a] which consistently gave 65-78% yields of **24** with little or no formation of by-products.[12] The precise mechanism by which fluoride ion catalyzes the cyclization of **22** to **24** is not known with certainty, but it presumably involves a strong hydrogen bond between F$^-$ and the hydrazide N-H group, with a corresponding increase in N-nucleophilicity.[11a,b] Interestingly, however, it appears likely that the active catalytic species in these, and related, cyclizations might actually be a decomposition product of *n*-Bu$_4$NF.[11c]

Once in hand the photochemical rearrangement of **24** to **25** took place under similar conditions to those employed for the achiral model systems **4** (300 nm, *t*-amyl alcohol, piperylene, -10° C, 20-48 h; *cf.* Scheme 1),[1] affording dihydropyrromethenones **25** as ~1:1 equilibrium mixtures of *E*- and *Z*-isomers. In analogous fashion, acetylenic acid **19b** (B = Me, Y = H) provided the enantiomeric dihydropyrromethenone **26b**, which within experimental error had equal but opposite $[\alpha]^{25}_D$ as that observed for **25b** (*Z*-isomers). These results are summarized in Table 1 (following page). As in the case with **4**,[1] satisfactory yields of **25** and **26** were only obtained in the presence of piperylene (triplet quencher), which minimizes the formation of by-products arising from hydrazide cleavage. In this connection, it is worth noting that benzyl ether **24d** (A = Me, B = *S*-CHOBnCH$_3$) and methyl ether **24c** (A = Me, B = *S*-CHOMeCH$_3$) showed markedly different behavior upon attempted photochemical rearrangement. Thus, **24c** afforded an ~40% yield of dihydropyrromethenone **25c** after 21 h at -10° C (300 nm), while **24d** reacted only very sluggishly to provide mainly the products of hydrazide cleavage

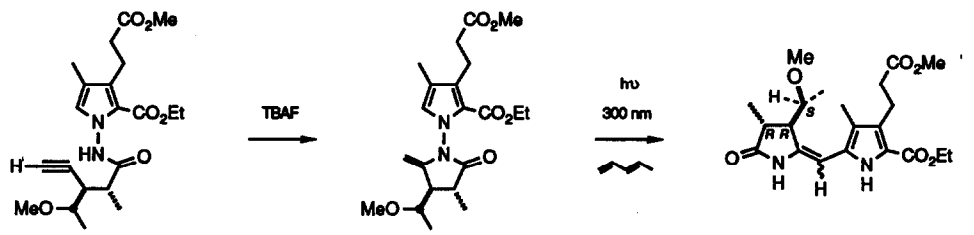
(<5% desired dihydropyrromethenone **25d** after 48 h). This result was not entirely unexpected, since **24d** contains a phenyl group which might be capable of internal triplet sensitization (*vide supra*).[11d] However, it serves to emphasize the fact that care must be taken in choosing protecting groups (R") for the C3' position.

Table 1

Compound	A	B	E:Z	Yield	Z-$[\alpha]^{25}_D$
25a	H	H	1:1	60% (75%)*	0.00°
25b	Me	Me	1:1	42% (47%)*	+40.18°, c = 5.50 (MeOH)
25c	Me	*S*-CHOMeCH$_3$	1:1	37%	- 20.82°, c = 8.21 (MeOH)
25d	Me	*S*-CHOBnCH$_3$	1:1	trace	-
26b	Me	Me	1:1	39% (47%)*	- 40.98°, c = 4.88 (MeOH)

* Yield based on recovered starting material

Finally, we were pleased to find that pyrrolohydrazide **27**, prepared in 89% yield from N-aminopyrrole **1a** (R = Me, R' = Et) and acetylenic acid **21c** (A = Me, B = *S*-CHOMeCH$_3$), could be converted in analogous fashion to enamide **28** (70%), and subsequently to homochiral dihydropyrromethenone **29** (46%; 60% based on recovered **28**). Dihydropyrromethenone **29** contains all of the functionality necessary for conversion to ring-A,B fragments of type **6**, and this last transformation is currently under active investigation.[13]



27 (89%) **28** (70%) **29** (46%, 60%*)

Z-$[\alpha]^{25}_D$ = -7.75°, c = 8.90 (MeOH)

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9. (a) The X-ray analysis of **21d** was carried out by Ms. Gayle Schulte of Yale University. (b) We are grateful to Doctor Douglas Fry, of Erskine College, for first preparing **21d**, and to Ms Maria C. Fermin, of Wesleyan University, for help with weighing air sensitive materials.
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12. As expected, enamides **24** exhibited atropisomerism due to hindered N-N bond rotation, although each isomer had identical photochemical behavior. See, for example: Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*, Springer-Verlag, Vienna-New York, 1989, p. 108.

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