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Tetrapyrroles. IV. A Highly Efficient Synthesis of Homochiral Dihydropyrromethenones *via* Pd^0 Mediated Coupling of Iodopyrroles and Acetylenic Amides

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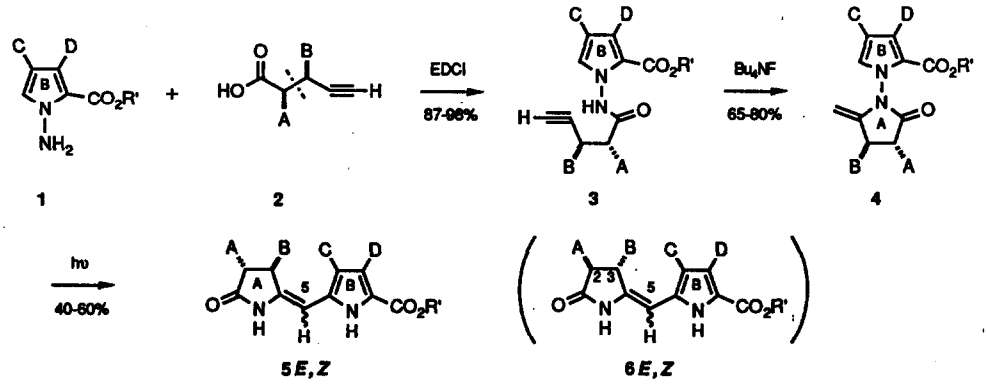
Abstract: *Homochiral dihydropyrromethenones of type 20 have been synthesized in a highly efficient manner by Pd^0 mediated coupling of iodopyrrole 14 with acetylenic amides 18, followed by F$^-$ catalyzed 5-exo-dig cyclization. In analogous fashion, phytochrome (8) precursor 25a has been prepared in 85% overall yield from iodopyrrole 22.*

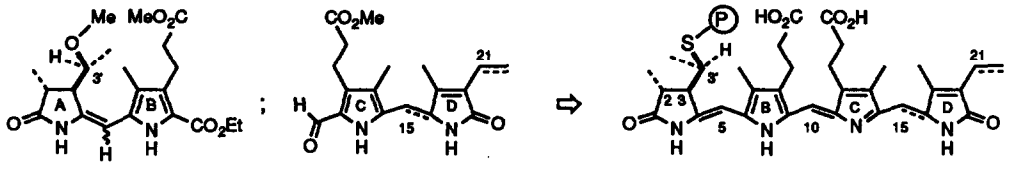
In the preceeding paper in this series we reported that acetylenic hydrazides of general structure **3** undergo a *n*-Bu_4NF catalyzed 5-*exo-dig* cyclization, affording enamides of type **4** which can be converted to homochiral dihydropyrromethenones **5*E,Z*** by photochemical 3,5-sigmatropic rearrangement (Scheme 1).[1] In



A,B = H, Me, *S*- and *R*-CHOMeCH$_3$, *S*- and *R*-CHOBnCH$_3$; C,D = H, Me, -(CH$_2$)$_4$-, Propionate; R' = Me, Et, Bn.

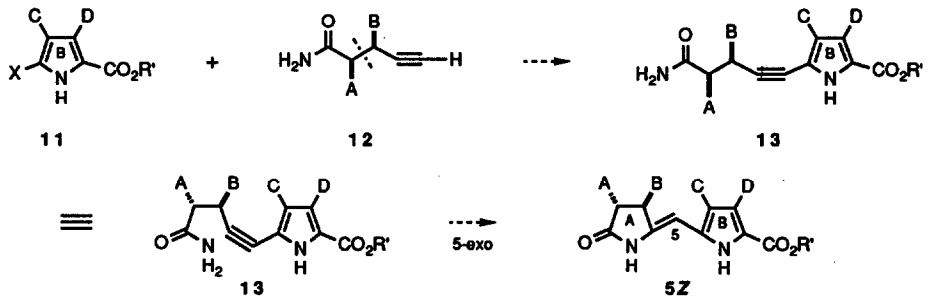
Scheme 1 (*Method A*)

analogous fashion, enantiomeric dihydropyrromethenones **6*E,Z*** were prepared from hydrazides ***ent*-3**, themselves derived by carbodiimide coupling of appropriate acetylenic acids ***ent*-2** with N-aminopyrroles **1** (*ent* = enantiomer of structure shown). Among other examples, this methodology was employed in the synthesis of dihydropyrromethenone **5a**, a potential ring-A,B precursor for the synthesis of biologically important tetrapyrroles such as phytochrome (**8**), phycocyanin (**9**) and phycoerythrin (**10**) (P = protein).[1]



The utility of this approach (*Method A*) stems partly from the fact that a wide variety of ring-A synthons **2** (and *ent*-**2**) are available by Nicholas-Schreiber reaction of chiral ester enolates with cobalt stabilized propargylic cations (dashed line in **2**, Scheme 1).[1,2] In addition, ring-B precursors of type **1** can now be prepared with unequivocal control over regiochemistry.[3] These developments provide for a considerable degree of flexibility in the introduction of substituents A-D. However, several shortcomings with this route have also arisen. For example, photochemical rearrangement of **4** to **5** invariably leads to ~1:1 mixtures of *E*- and *Z*-isomers at C4-C5, while the natural stereochemistry at this position is *Z*. Also, protecting groups must be chosen with care to avoid complications arising from triplet-sensitized hydrazide cleavage.[1] And finally, yields, although good (40-60%), have been optimized and there is probably little opportunity for improvement.

Our discovery of the F^- catalyzed cyclization of unactivated acetylenic hydrazides of type **3** raised the possibility of an attractive modification of our original strategy which earlier had been considered impractical. In this approach (*Method B*), acetylenic pyrroles of type **13**, in principle available *via* Sonogashira coupling of halopyrroles **11** with acetylenic amides **12**,[4] would be directly converted to dihydropyrromethenones **5-Z** by 5-*exo-dig* cyclization (Scheme 2). As in our original strategy (*Method A*, Scheme 1), *Method B* makes use of a

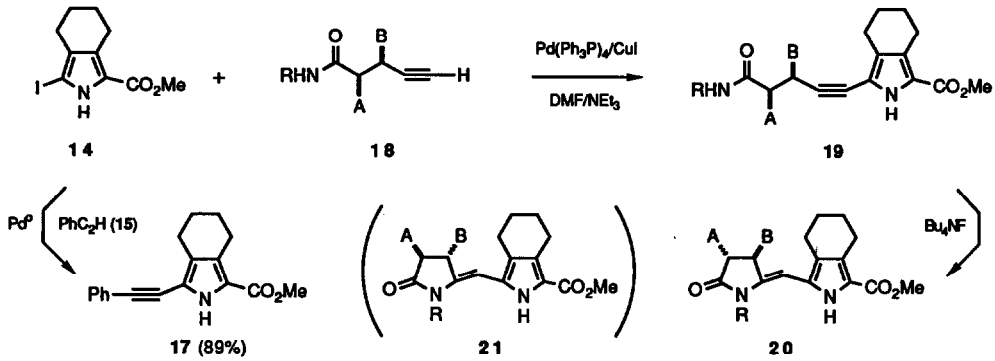


Scheme 2 (*Method B*)

Nicholas-Schreiber reaction for preparing the ring-A synthon **12** in homochiral form and with unequivocal control over stereochemistry at C2, C3 and C3'. However, a significant advantage of *Method B* is the fact that bond connectivity between C5 and C6 would be established directly, thereby eliminating the need for a subsequent 3,5-sigmatropic rearrangement. Also, it seemed likely that kinetic control in the amide addition to the acetylenic triple bond would lead directly to the naturally occurring *Z*-configuration at C4-C5 (*vide supra*).

At the time we began this work, only scattered reports had appeared describing the coupling of acetylenes with halopyrroles,[5] and few provided experimental details. Therefore, our initial studies in this area were carried out with the model iodopyrrole **14**,[6a] which afforded a 21% yield of pyrroloacetylene **17** upon coupling with phenylacetylene (**15**) using the reagent combination $PdCl_2(Ph_3P)_2$/CuI in NEt_3 as solvent (mmoles: 1.0 **14** : 1.1 **15** : 0.1 $PdCl_2(Ph_3P)_2$: 0.1 CuI ; 3.0 ml NEt_3, 5-16 h, 22° C) (Scheme 3, following page).[4] The major by-product in this case was the *bis*-acetylene PhC≡C-C≡CPh (**16**) arising from oxidative dimerization of **15**. Similar results were obtained using $Pd(PPh_3)_4$ and most other Pd^0 catalysts, although modest improvements were observed with $Pd[P(o\text{-Tolyl})_3]_4$.[7] A number of variations in solvent (THF, MeCN, DMF) and molar ratio of **14**:**15** were also explored, all with the catalyst system $Pd(PPh_3)_4$/CuI/NEt_3. In general, DMF provided the cleanest reactions,[8] while ratios of **15**:**14** as high as 2:1 afforded slight increases in yields of coupling product **17**, together with much larger quantities of dimer **16**. However, by far the most important factor influencing yields in these reactions was the presence or absence of oxygen: *At least three freeze-thaw cycles are necessary for optimum yields of* **17** *and to minimize formation of* **16**.[9] Thus, our best results were obtained with a ratio of **14**:**15** = 1.0:1.1, using DMF as solvent under rigorously degassed conditions (mmoles: 1.0 **14** : 1.1 **15** : 0.1 $Pd(Ph_3P)_4$: 0.22 CuI : 3.0 NEt_3; 3 ml DMF, 5-21 h, 22° C). This protocol consistently afforded yields of **17** in excess of 85% with little or no dimer formation. In identical fashion, coupling of iodopyrrole **14** with the more complex acetylenic amides **18a-e** afforded the corresponding pyrroloacetylenes **19a-19e** in yields of 88-

98%; and finally, coupling of *ent*-**18c** (**A,B** = Me; **R** = H) with **14** gave a 95% yield of the enantiomeric pyrroloacetylene *ent*-**19c**, again in homochiral form. These conditions appear to be general for the Sonogashira coupling of 1*H*-2-iodopyrroles with acetylenes.[5e]



14 **18** **19** **17 (89%)** **21** **20**

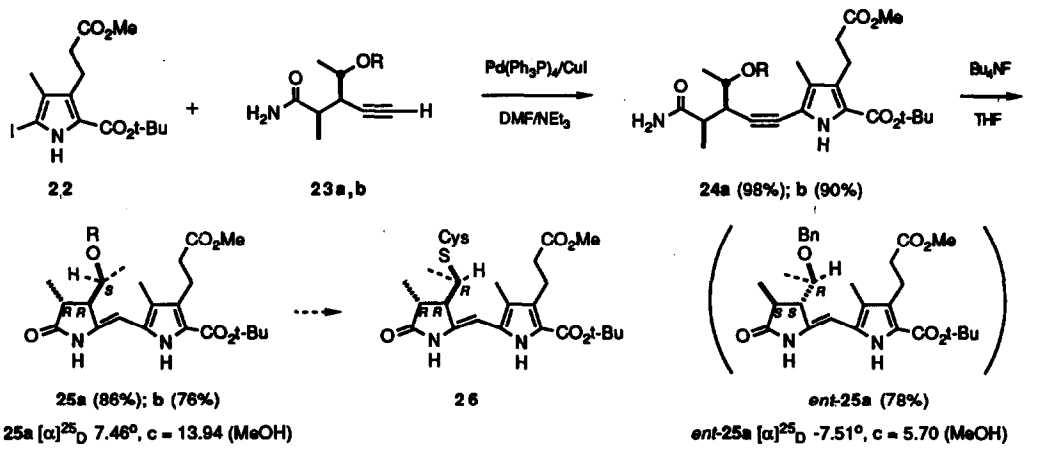
Compound	A	B	R	Yield	$[\alpha]^{25}_D$ 20c-e; 21c
19a (20a)	H	H	Bn	93% (42%)	0.00°
19b (20b)	H	H	H	88% (25%)	0.00°
19c (20c)	Me	Me	H	98% (83%)	41.52°, c = 3.30 (MeOH)
19d (20d)	Me	*S*-CHOMeCH$_3$	H	89% (78%)	-20.46°, c = 6.84 (MeOH)
19e (20e)	Me	*S*-CHOBnCH$_3$	H	93% (75%)	8.14°, c = 5.28 (MeOH)
ent-19c (21c)	Me	Me	H	95% (81%)	-41.00°, c = 2.58 (MeOH)

Scheme 3

Once in hand, cyclization of pyrroloacetylenes **19c-e** and *ent*-**19c** occurred under substantially the same conditions as those employed in the conversion of acetylenic hydrazide **3** to cyclic enamide **4** (6 eq *n*-Bu$_4$NF, THF, reflux, 24-48 h), affording *Z*-dihydropyrromethenones **20c-e** and **21c** in 75-83% yield (unoptimized), with no trace of the corresponding *E*-isomers (Scheme 3). The materials thus obtained were identical in both physical properties and optical rotation to the corresponding *Z*-isomers previously prepared by *Method A*.[1] Certain features of this cyclization are worthy of special note. First, for maximum yield it is essential that cyclization be carried out under strictly anoerobic conditions (≥ three freeze-thaw cycles). Second, cyclization occurs faster with more highly substituted substrates (rate: **A,B** = Me,*S*-CHORCH$_3$ ≈ Me,Me > H,H [*cf.* **20a,b**]), and is extremely slow with simple aliphatic acetylenic amides and hydrazides lacking a conjugated pyrrole ring. Finally, all of these cyclizations exhibit a brief induction period (~45 min) prior to the onset of reaction. This last characteristic led us to examine the effect of known decomposition products of *n*-Bu$_4$NF on reaction rates,[10] and we have evidence to suggest that the actual catalytic species in these cyclizations is the thermodynamically stable *n*-Bu$_4$N$^+$FHF$^-$ complex ("tetra-*n*-butylammonium bifluoride"). This material forms rapidly upon heating *n*-Bu$_4$NF in solution and upon attempted drying of *n*-Bu$_4$NF·3 H$_2$O at 40-70° C.[10a] Indeed, it seems likely that *n*-Bu$_4$N$^+$FHF$^-$ is also involved in other F$^-$ catalyzed reactions which specify the use of TBAF at T > 40° C.[10b,c]

Finally, we were pleased to find that *Method B* was also highly effective for the synthesis of dihydropyrromethenones related to tetrapyrroles **8-10** (Scheme 4, following page). Thus, in a noteworthy two-step sequence, Pd° catalyzed coupling of the readily available iodopyrrole **22**[11a,b] with the homochiral amide **23a** (**R** = Bn) gave a virtually quantitative yield of the acetylenic pyrrole **24a**, which upon F$^-$ induced cyclization as described above afforded the ring-A,B precursor **25a** in 86% yield. In identical fashion, but beginning with *ent*-**23a** (**R** = Bn), enantiomer *ent*-**25a** was prepared in homochiral form and with $[\alpha]^{25}_D$ of essentially equal magnitude but opposite sign. Similar yields of **25b** were obtained starting with acetylenic amide **23b** (**R** = Me).

The results summarized in Schemes 3 and 4 are considerably better than those obtained following *Method A* (Scheme 1),[1] and we believe that this methodology has significant advantages over any other that is currently



Scheme 4 (a: R = Bn; b: R = Me)

available. In the following paper in this series we describe the application of this approach to the synthesis of the C,D-ring fragments of phytochrome (**8**) and phycocyanin (**9**).[11a,12]

References and Notes

1. Jacobi, P. A.; Rajeswari, S., preceeding paper in this series.
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5. (a) Vasilevskii, S. F.; Sundukova, T. A.; Shvartsberg, M. S.; Kotylarevskii, I. L. *Bull. Acad. Sci. USSR Div. Chim. Sci.* **1979**, 1536 (English translation; p 1661 in Russian); *cf. Chem. Abstr.* **1979**, *91*, 157544g. (b) *Ibid.* **1980**, 1871; *cf. Chem. Abstr.* **1981**, *94*, 30464n. Very recently, Muchowski *et al.* have described a procedure which requires heating at reflux in NEt_3/MeCN: (c) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653. See also, (d) Chen, W. *Ph.D. Dissertation*, Department of Chemistry, University of Alabama, Tuscaloosa, Alabama, 1990. (e) Preliminary results indicate that coupling is much slower with 1-BOC-2-iodopyrroles.
6. (a) Iodopyrrole **14** was prepared by iodination of 2-carbomethoxy-3,4-cyclohexylpyrrole (NIS, 89%), itself derived in 72% yield from 1-nitrocyclohexene and $NCCH_2CO_2Me$ using the methodology of Barton *et al.*: (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.
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8. Robins, M. J.; Vinayak, R. S.; Wood, S. G. *Tetrahedron Lett.* **1990**, *31*, 3731.
9. This effect has also recently been commented on by Magnus *et al.*: Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.
10. (a) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112. (b) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644. (c) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.
11. Iodopyrrole **22** was initially prepared by iodination of *tert*-butyl 3-[2'(methoxycarbonyl)ethyl]-4-methyl-pyrrole-2-carboxylate (NIS, 47%), itself derived in 51% yield using the methodology of Barton *et al.* (Ref. 6b): (a) Jacobi, P.A.; DeSimone, R. W., following paper in this series. However, for large scale preparations we have found that the recent modification of Smith's procedure[11c] by Rapoport is more convenient: (b) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. (c) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1971**, 502. (d) NOTE: The melting point for **22** has been reported as 133-34° C upon crystallization from 60-80° petroleum ether.[11c] We find that **22** prepared by both methods described above melts sharply at 86-87° C after repeated crystallization (Et_2O/30-60° pet ether) and drying 24 h over P_2O_5.

12. Financial support of this work by NIH Grant # GM38913 is gratefully acknowledged.

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