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An Improved Synthesis of the C,D-Ring Pyrromethenone of Phytochrome and Phytochromobilin

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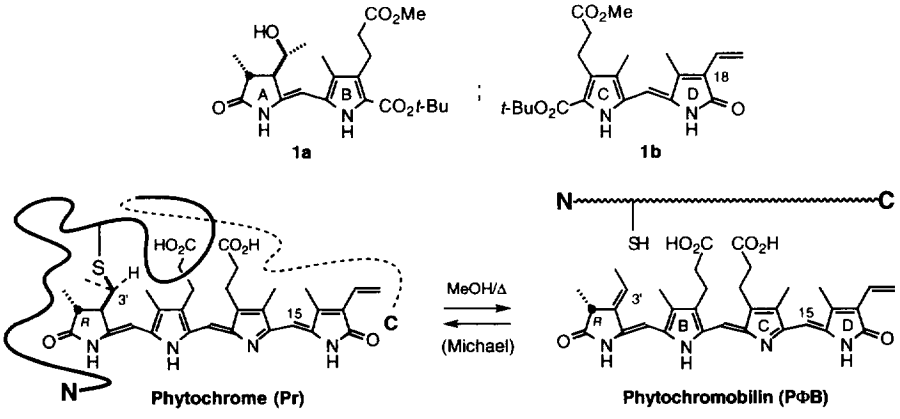
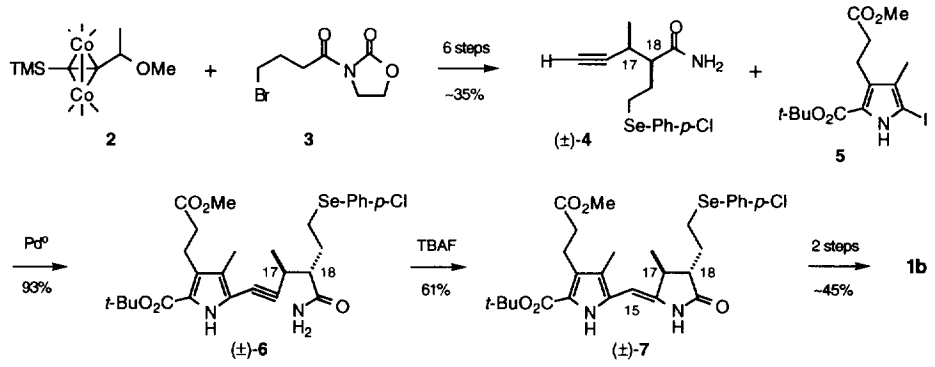
Abstract: Pyrromethenone **1b**, the C,D-ring segment of both phytochrome (**Pr**) and phytochromobilin (**PΦB**) has been prepared in a highly efficient fashion beginning with 2-acetylbutyrolactone (**8**). The key steps involved conversion of **8** to the *Z*-enol triflate **9**, followed by Pd^0 catalyzed coupling with trimethylsilylacetylene, *p*-chlorophenylselenide ring opening, and amidation, to afford ring-D synthon **11** having the proper geometry and oxidation state for conversion to **1b**.

In preceding papers in this series we described novel syntheses of the pyrromethenone derivatives **1a** and **1b**,[1a,b] which are attractive precursors for the A,B- and C,D-ring segments, respectively, of the biologically important plant pigment phytochrome (**Pr**).[2] The identical C,D-ring pyrromethenone **1b** is found in phytochromobilin (**PΦB**), obtained from **Pr** by thermolysis in MeOH.[2b] Interest in **PΦB** derives from the fact that *in vitro* reconstitution of **PΦB** with its apoprotein **N-C** occurs in an autocatalytic fashion, affording **Pr** having identical photochemical properties as the native protein/chromophore complex.[3a] This discovery opens the possibility for incorporation of labeled **PΦB** to study the process of photomorphogenesis at the molecular level, in particular the question of geometrical isomerization at C_{15}.[3b,c]



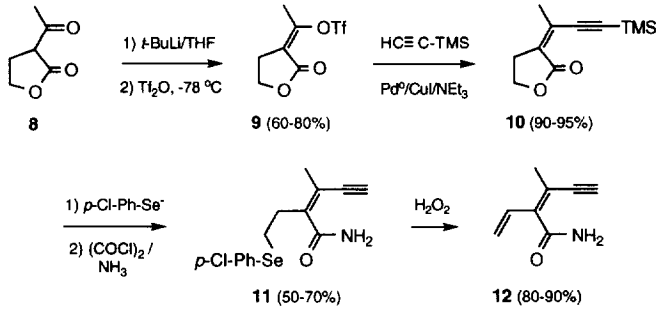
A key intermediate in our earlier synthesis of **1b** was the acetylenic amide (±)-**4**, which was prepared in six steps from cobalt complex **2** and achiral oxazolidinone **3** (Scheme 1, following page).[1b] This route made use of a Nicholas-Schreiber condensation for effecting C_{17}-C_{18} bond formation (**Pr** numbering).[4] The utility of (±)-**4** as a D-ring synthon was then demonstrated by Sonogashira coupling with iodopyrrole **5** to give acetylenic pyrrole (±)-**6**,[5] which upon F^- catalyzed 5-*exo-dig* cyclization afforded the dihydropyrromethenone (±)-**7** in ~60% yield (TBAF = *n*-$Bu_4N^+F^-$).[1] Finally, (±)-**7** was converted to the target pyrromethenone **1b** by a two step sequence involving DDQ oxidation and selenoxide elimination.[1b,6]



Scheme 1

Although this synthesis was successful, a number of considerations led us to seek a more direct route to **1b**. Foremost among these was the issue of efficiency, which is particularly important in preparing ^{13}C labeled derivatives for reconstitution (*vide supra*). Even after optimization, the length of the synthesis impeded the preparation of **1b** in the quantities necessary for our studies (ten steps not including preparation of starting materials **2** and **3**). In part, this deficiency is a consequence of employing a strategy based upon the Nicholas-Schreiber condensation (*i.e.* **2** + **3** --> **4**), which is the method of choice for preparing *syn*-adducts of type **4** in enantiomerically pure form.[1,4] A similar approach was efficiently utilized in our enantioselective synthesis of **1a**,[1a] which has three stereogenic centers. In the present case, however, this strategy incorporates an unnecessary level of complexity, since the ultimate target **1b** is devoid of stereochemical features. The stereocenters which are introduced at C_{17} and C_{18} in (±)-**4** must eventually be destroyed by oxidation of (±)-**7**.

As an alternative approach, we have now developed unambiguous syntheses of the unsaturated acetylenic amides **11** and **12**, which have both the correct oxidation state and double bond geometry for ultimate conversion to **1b** (Scheme 2). These syntheses are noteworthy for their efficiency (three steps for **11**; four

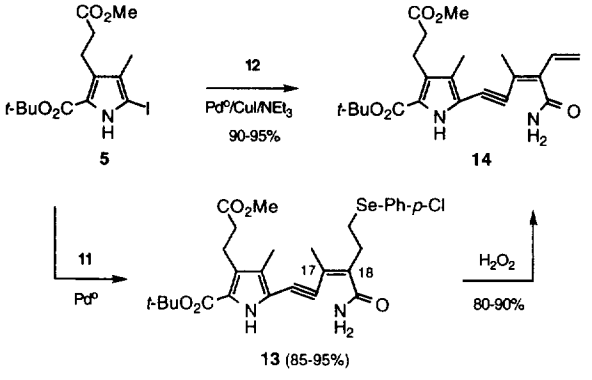


Scheme 2

steps for **12**) and make use of inexpensive starting materials.[7a] As the key step in our synthesis of **11**, enolization of 2-acetylbutyrolactone (**8**) with *t*-BuLi at -78 °C took place with excellent selectivity, affording, after quenching with triflic anhydride (Tf_2O), a 60-80% yield of *Z*-enol triflate **9** as the only detectable isomer (yields represent a range from many experiments). Selectivity in this case presumably is due to Li^+ coordination with the enolate anion derived from **8**, in exact analogy to the work of Brückner, Suffert *et al.* with 2-formylbutyrolactone.[8a] Sonogashira coupling of **9** with trimethylsilylacetylene then gave a 90-95% yield of the acetylenic lactone **10**,[5] which correctly sets the double bond geometry as *Z*. Next, acetylenic lactone **10** was readily converted to the acetylenic amide **11** by initial S_N2 ring opening with sodium *p*-chlorophenylselenide,[9]

followed by amidation of the resultant carboxylic acid with $(COCl)_2/NH_3$ (50-70% overall yield). Amide **11** is a stable crystalline solid which we have routinely prepared on multigram scales. Finally, oxidation of **11** with H_2O_2 led to smooth selenoxide elimination, producing the alkene derivative **12** as an unstable solid prone to polymerization (80-90%).

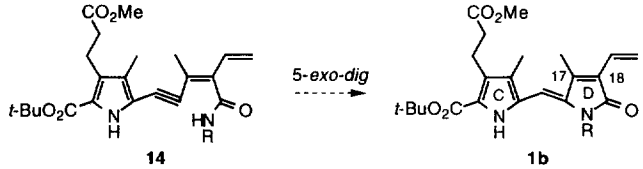
Two routes were explored for preparing the acetylenic pyrrole **14**, our anticipated precursor to pyrromethenone **1b** (Scheme 3). The first of these made use of a Sonogashira coupling of iodopyrrole **5** with



Scheme 3

the unsaturated acetylenic amide **12**,[5] which afforded **14** in 90-95% yield on relatively small scales (< 1 g). The success of this reaction depends upon employing only freshly prepared **12**, since this material polymerizes rapidly even when stored at 0 °C. For larger scale reactions (> 1 g), it was generally more convenient to delay oxidative elimination until the last stage of the synthesis. Thus, Pd^0 catalyzed coupling of acetylenic amide **11** with **5** gave a 85-90% yield of the stable acetylenic pyrrole **13**, which upon treatment with H_2O_2 was cleanly converted to the unsaturated derivative **14**.

Finally, numerous conditions were evaluated to carry out the requisite 5-*exo-dig* cyclization leading from **14** to the pyrromethenone **1b** (Scheme 4). As in our previous studies, no cyclization was observed using Pd (II) as a catalyst,[1c] nor with Montmorillonite K10 clay,[10] or CsF absorbed on silica gel (entries 1-3). Some measure of success was achieved employing a large excess of TBAF (> 6 eq),[1a,b] which afforded ~40% of **1b** after 96 hours at reflux in THF (entry 4). Under these conditions, however, substantial decomposition also

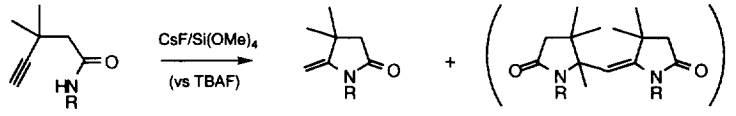


Entry	Reagent	Cond.	Yield
1	Pd (II)	RT/48 h	0%
2	Mont. clay	Δ/$CHCl_3$/13 h	0%
3	CsF/silica	Δ/THF/48 h	0%
4	TBAF	Δ/THF/96 h	40%
5	TBAF/Al_2O_3	Δ/THF/24 h	25%
6	F^-/polymer	Δ/THF/13 h	0%
7	CsF/$Si(OMe)_4$	Δ/THF/6 h	60%

Scheme 4

occurred. No improvement was observed with various modified TBAF reagents, including TBAF/Al_2O_3 (entry 5, 25%), and Amberlyst A-26 quaternary ammonium fluoride resin (entry 6, 0%).[7b] By far the best results were obtained with the reagent system CsF/$Si(OMe)_4$ (entry 7), which was initially introduced by Corriu and Perz as a catalyst for Michael additions.[11a] In the present case, cyclization of **14** with 5 eq CsF/20 eq $Si(OMe)_4$ gave a 60% yield of **1b** after only 6 hours heating in THF, in dramatic contrast to the results obtained with TBAF (entry 4).[6b] The only byproduct was a small amount of the corresponding dimethylester obtained by transesterification.

As previously suggested,[11a] the active catalyst in this reaction might involve a pentacoordinated silicon species formed by nucleophilic attack by F^- on $Si(OMe)_4$.[11a] In any event, some indication of the power of this reagent is given by the fact that even unactivated acetylenic amide **15a** (R = H) gave a 43% yield of cyclic enamide **16a** (R = H), together with 54% of dimer **17a** (R = H), upon heating 5 hours in toluene (2 eq CsF/5 eq Si[OMe]$_4$). Previously, **16a** was obtained in ~5% yield after heating 48 hours with TBAF.[1c] In similar fashion, benzyl amide **15b** (R = Bn) gave a 89% yield of enamide **16b** (R = Bn) after 1 hour heating in toluene.



15a (R = H)
15b (R = Bn)

16a (43% vs. 5%)
16b (89%)

17a (54%)
17b (0%)

The synthesis of **1b** outlined above is less than half the length of our previous synthesis and it does not require the use of expensive cobalt reagents. Moreover, it should be readily adaptable to the preparation of specifically labeled substrates. Experiments in this direction are currently in progress.[7c,12]

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