Tetrapyrroles. V. Formal Syntheses of the Ring-C,D Pyrromethenones of Phytochrome and Phycocyanin

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Abstract: Formal syntheses of pyrromethenones 2 and 3, potential intermediates for the preparation of phycocyanin (5) and phytochrome (4), respectively, have been accomplished by Pd⁰ mediated coupling of iodopyrrole 7 with acetylenic amides of general structure 8a,b, followed by F- catalyzed 5-exo-dig cyclization and DDQ oxidation.

In the preceeding paper in this series we described a highly efficient synthesis of dihydropyrromethenone 1,[1] an attractive ring-A,B precursor for the preparation of biologically important tetrapyrroles such as phytochrome (4), phycocyanin (5) and phycoerythrin (6). During the course of this work new methodology
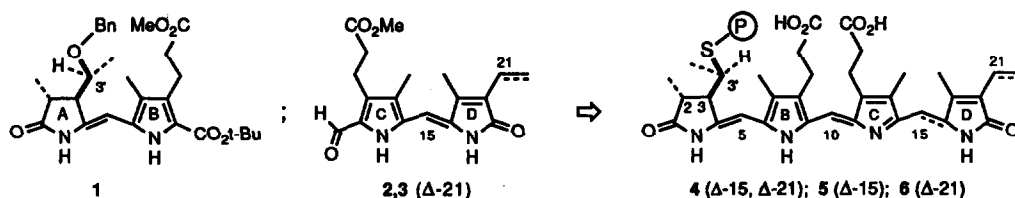

was developed for the unambiguous control of both relative and absolute stereochemistry at C2, C3 and C3', as well as double bond geometry at C4-C5 to give exclusively the Z-isomer. This last issue is of importance since current models for photoactivation of 4 postulate a reversible Z,E-isomerization about either C4-C5,[2a] or, most recently, C15-C16.[2b] In this note we describe formal syntheses of ring-C,D pyrromethenones 2 (sat'd C21) and 3 (Δ-C21) following the general strategy outlined in Scheme 1. These materials have previously been employed
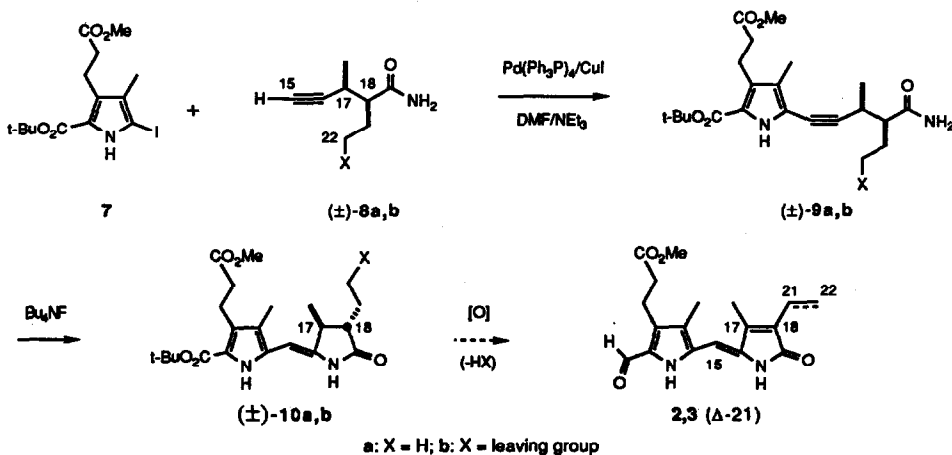
Scheme 1

in the synthesis of a variety of model systems related to **4** and **5**,[3] and they are potential intermediates for the synthesis of the naturally occurring substances. As indicated, the key steps in our projected syntheses of **2** and **3** closely follow the precedent set in our synthesis of **1**,[1,4] with the exception that absolute stereochemistry at C17 and C18 in **8-10** is immaterial since these centers are ultimately oxidized.
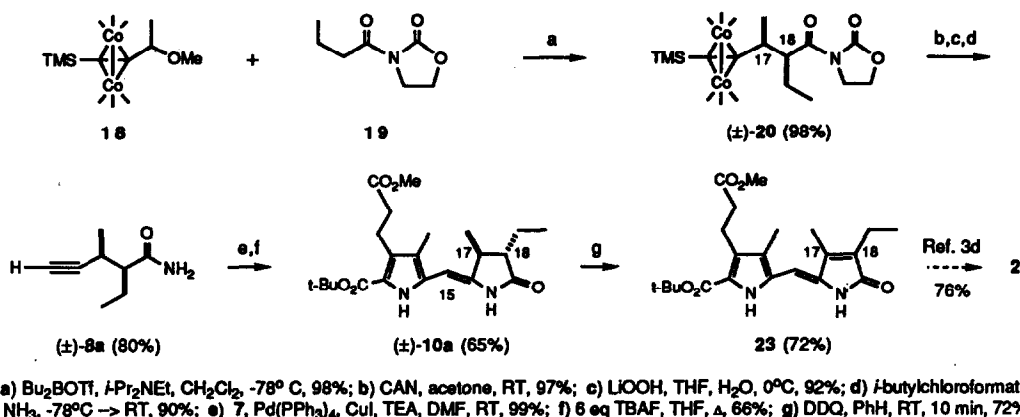
Iodopyrrole **7** was conveniently prepared by either of the routes summarized in Scheme 2. The first of these makes use of the methodology of Barton *et al.*,[5] and has the advantage of flexibility in the choice of ester group R'. Thus, ester aldehyde **11** was readily converted to the Henry adduct **13** by DBU catalyzed condensation with nitroethane (**12**) followed by trapping with acetic anhydride (71%). This last material then underwent base catalyzed elimination of HOAc, followed by reaction with the appropriate isocyanoacetic ester **14**, to afford unstable adducts of type **15** which rapidly aromatized to give the desired pyrroles **16**.[5] A wide

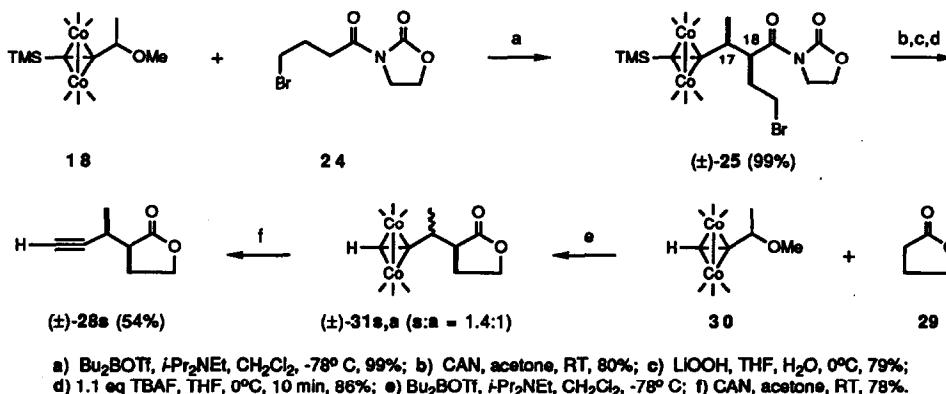a: R' = Et; b: R' = *t*-butyl
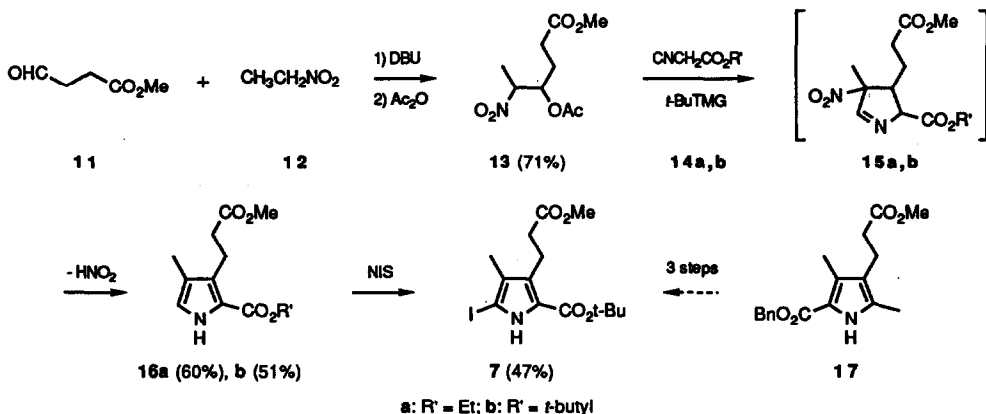
Scheme 2

range of base/solvent combinations was explored in order to optimize the transformation of **13** to **16**, and we eventually found that the system *t*-butyltetramethylguanidine/*i*-propyl alcohol consistently gave the best yields of both **16a** (60%) and **16b** (51%).[5] Iodination of **16b** with NIS then gave a 47% yield of the ring-C precursor **7** on a 0.5-1 g scale. As an alternative approach to **7**, Rapoport *et al.* have recently described a modification of the procedure of Smith *et al.* which involves oxidative degradation of benzyl ester **17**.[6a,b] Although this sequence is somewhat longer, it works quite well for preparing **7** on multigram scales (>5 g).

As in our previous studies with **1**,[1] we made use of a Nicholas-Schreiber reaction for preparing the acetylenic amide (±)-**8a**,[7] employing in this case the achiral oxazolidinone **19** since control of absolute stereochemistry at C17-C18 was not important (Scheme 3, following page). Thus, dibutylborontriflate/*i*-Pr$_2$NEt catalyzed condensation of **19** with the cobalt complex **18**[7b] gave a 98% yield of the Nicholas adduct (±)-**20**,[7a] which by NMR analysis had exclusively *syn*-stereochemistry at C17-C18 (determined after decomplexation). Adduct (±)-**20** then afforded an 80% overall yield of the target amide (±)-**8a** by a straightforward sequence of steps involving cobalt cleavage to give the corresponding acetylene **21** (ceric ammonium nitrate [CAN],[7a] 97%), imide hydrolysis with concomitant TMS removal (92%),[8] and amidation of the resultant carboxylic acid **22** *via* the mixed *i*-butylcarbonate derivative (90%). It is important to note that simple alkyl esters corresponding to **19** gave much lower yields of Nicholas adducts and showed little selectivity between *syn*- and *anti*-stereochemistry at C17-C18. Once in hand, acetylenic amide (±)-**8a** was cleanly converted to the dihydropyrromethenone (±)-**10a** by Pd° coupling with iodopyrrole **7** (99%), followed by F⁻ catalyzed 5-*exo-dig* cyclization (Z-isomer only, 65% overall yield from **7**).[1] Finally, oxidation of (±)-**10a** with DDQ gave a 72% yield of pyrromethenone **23** as a yellow, crystalline solid (plates from MeOH, mp 207-208° C [lit.[3a] mp 206-208° C]), which had identical spectral data as that reported in the literature.[3a] Since Rapoport *et al.* have previously converted **23** to **2** by decarboxylative formylation (76%),[3d] this step completed the formal total synthesis of phycocyanin precursor **2**.
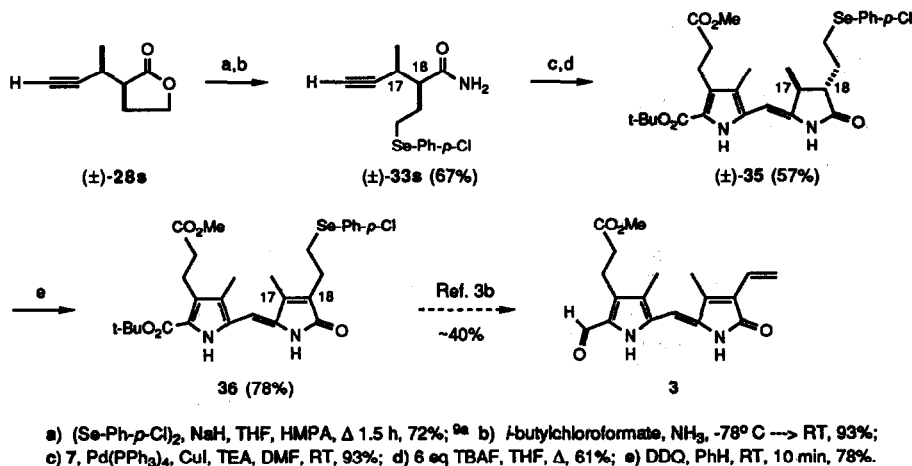
a) Bu$_2$BOTf, i-Pr$_2$NEt, CH$_2$Cl$_2$, -78° C, 98%; b) CAN, acetone, RT, 97%; c) LiOOH, THF, H$_2$O, 0°C, 92%; d) i-butylchloroformate, NH$_3$, -78°C --> RT, 90%; e) 7, Pd(PPh$_3$)$_4$, CuI, TEA, DMF, RT, 99%; f) 6 eq TBAF, THF, Δ, 66%; g) DDQ, PhH, RT, 10 min, 72%.

Scheme 3

The key intermediate for our synthesis of pyrromethenone **3** was the acetylenic lactone (±)-**28s** (Scheme 4, s = *syn*; a = *anti*), which incorporates all of the features necessary for elaboration to amides of general structure (±)-**8b** (*cf.* Scheme 1). Two routes were explored for the synthesis of (±)-**28s**, the first of which closely followed the precedent established in preparing (±)-**8a** (*cf.* Scheme 3). Thus, condensation of cobalt complex **18** with the achiral oxazolidinone **24** afforded a virtually quantitative yield of the Nicholas adduct (±)-**25** (99%, *syn*-isomer only), which gave an 80% yield of the corresponding acetylene (±)-**26** upon decomplexation with CAN. Next, we were pleased to find that imide hydrolysis of (±)-**26** led to concomitant bromide displacement and lactonization,[8] affording a 54% overall yield of the target lactone (±)-**28s** after TMS group cleavage with TBAF. Alternatively, lactone (±)-**28s** was also prepared by direct alkylation of

a) Bu$_2$BOTf, i-Pr$_2$NEt, CH$_2$Cl$_2$, -78° C, 99%; b) CAN, acetone, RT, 80%; c) LiOOH, THF, H$_2$O, 0°C, 79%; d) 1.1 eq TBAF, THF, 0°C, 10 min, 86%; e) Bu$_2$BOTf, i-Pr$_2$NEt, CH$_2$Cl$_2$, -78° C; f) CAN, acetone, RT, 78%.

Scheme 4

butyrolactone (**29**) with cobalt complex **30**, but in this case *syn*-selectivity was poor (78% overall yield, *syn:anti* = 1.4 : 1). Interestingly, *syn*-selectivity in the alkylation of lactone **29** with TMS-substituted cobalt complex **18** dropped to s:a = 1.0 : 3.4, the reverse of the trend previously noted by Schreiber[7a] and us[1] for Nicholas alkylations using boron enolates of acyl oxazolidinones. In principle both *syn*- and *anti*-isomers of **28** are suitable precursors for the synthesis of **3**. However, in practice we have found that *anti*-amides corresponding to **9b** undergo 5-*exo-dig* cyclization to enamides only with great difficulty, presumably due to steric congestion in the transition state leading to ring closure. Therefore this last route was not pursued further.

Acetylenic lactone (±)-28s was readily converted to the acetylenic amide (±)-33s by initial S_N2 ring opening with sodium p-chlorophenylselenide (72%),[9] followed by amidation of the resultant carboxylic acid (±)-32 with i-butylchloroformate/NH_3 (93%, Scheme 5). Amide (±)-33s then gave a 57% overall yield of dihydropyrromethenone (±)-35 upon Pd^o mediated coupling with 7 (93%) followed by F^- induced cyclization (Z-isomer only).[1] Finally, as described above for (±)-10a (Scheme 3), oxidation of (±)-35 with DDQ afforded a 78% yield of pyrromethenone 36 as a yellow, crystalline solid (plates from CH_2Cl_2/Et_2O/hexanes, mp 194-195° C [lit.[3b] mp 195° C]), which had identical spectral data as that reported in the literature.[3b] Since Gossauer et al. have previously converted 36 to 3 by selenoxide elimination followed by decarboxylative formylation (39% overall yield),[3b] this last step completed the formal total synthesis of phytochrome precursor 3.

(±)-28s (±)-33s (67%) (±)-35 (57%)

36 (78%) 3

a) $(Se-Ph-p-Cl)_2$, NaH, THF, HMPA, Δ 1.5 h, 72%;[9a] b) i-butylchloroformate, NH_3, -78° C ⟶ RT, 93%; c) 7, $Pd(PPh_3)_4$, CuI, TEA, DMF, RT, 93%; d) 6 eq TBAF, THF, Δ, 61%; e) DDQ, PhH, RT, 10 min, 78%.

Scheme 5

In closing, it is worth noting that the methodology described in these papers[1] is comparable in function to the Eschenmoser sulfide-contraction procedure for the synthesis of vinylogous amidines.[10] We believe it might also be employed in an iteritive fashion for the enantiospecific synthesis of complex macrocyclic tetrapyrroles of the chlorin, isobacteriochlorin, and corrin class, and this possibility is currently under active investigation.[11]

References and Notes

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