Iterative Synthesis of Semicorrins, Tripyrrolines, and Higher Analogues

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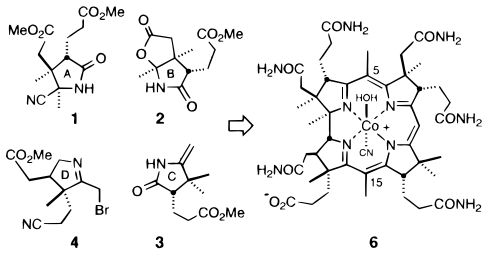
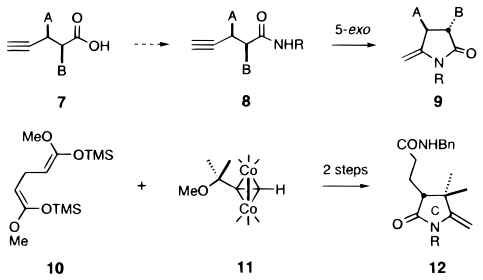
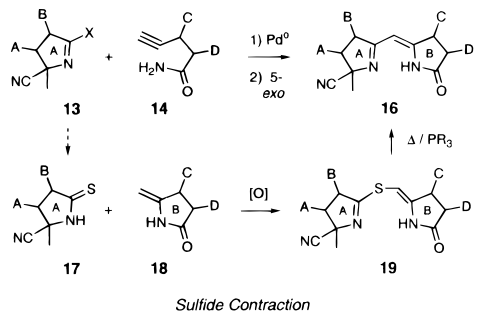
Hydroporphyrins of the chlorin, bacteriochlorin, and corrin families are ubiquitous chromophores in nature, and they play important roles in many biological processes.[1] Also, chlorins and bacteriochlorins are promising substrates for use in tumor photodynamic therapy (PDT).[2] The most complex members of this group are the corrins, which incorporate up to 10 stereogenic centers within the macrocycle. A noteworthy accomplishment in this area was the elegant synthesis of cobyric acid (**6**) by Eschenmoser et al.[3a]



Recently we have shown that alkyne acids **7** are versatile precursors to cyclic enamides of type **9** (R = Bn), via initial amidation to alkyne amides **8**, followed by 5-*exo*-*dig* cyclization.[5,6] As one example, enantiomerically pure enamides **9a** and *ent*-**9a** (A,B = Me; R = Bn) were obtained in ∼90% yield upon brief warming of **8a** or *ent*-**8a**, respectively, with 1.0 M TBAF/THF (*ent* = mirror image of structure shown). In analogous fashion, racemic enamide (±)-**12a** (R = Bn) was prepared in two steps starting with the bis-ketene silyl acetal **10** and alkyne cobalt complex **11** (∼75% overall yield).[5a] Enamide (±)-**12a** has the substitution pattern found in ring-C of vitamin B_{12}, and it was cleanly debenzylated to the parent enamide (±)-**12b** (R = H) with Na/NH_3 (98% yield).



In principle, cyclizations of type **8** → **9** might be employed in an iterative synthesis of hydroporphyrins, taking advantage of the high reactivity of iminoyl derivatives of general structure **13** (X = Cl, OTf, etc.). We expected that intermediates **13** could be derived from enamides **9** (R = H) by initial double bond protection with KCN,[3] followed by activation of the lactam carbonyl group. Pd(0)-mediated coupling of **13** with a second alkyne amide **14** should then yield the corresponding pyrrolinoalkyne **15** (not shown),[6a,7] which upon 5-*exo*-*dig* ring closure would give semicorrin **16**. Finally, repetition of this three-step sequence of enamide activation, alkyne coupling, and cyclization could afford tripyrrolines and ultimately secocorrins. This strategy complements the sulfide contraction methodology involving oxidative coupling of thiolactams **17** and enamides **18**, followed by PR_3-induced extrusion of sulfur.[4]



Sulfide Contraction

This concept was first tested with the enamide derivative **21b**, itself derived by 5-*exo*-*dig* cyclization of the alkyne acid **20a** ($PdCl_2$, 100%),[8] followed by aminolysis (NH_3, −78 °C, vacuum dehydration, 87%).[9] (Scheme 1). Enamide **21b** was then readily converted to the iminoyl chloride **23** by initial protection with KCN (90%),[3] followed by chlorination using Ph_3P/CCl_4 (85%).[10] Finally, we were pleased to find that Sonogashira coupling of **23** with the alkyne amide **8c** (R = H; A,B = Me) afforded a 70% yield of the pyrrolinoalkyne **24**,[7] which underwent clean cyclization with TBAF to afford the semicorrin **25** (epimers at C_2).[6a] Cyclization of **24** occurs readily at rt due to the activating influence of the ring-A imine.

We next studied the coupling of the iminoyl chloride **23** with the alkyne amide **20b**, which was accomplished in 89% yield using the reagent system Pd(0)/CuI. The resultant pyrrolinoalkyne **26** was then cleanly converted to the *Z*-semicorrin **27** upon treatment with TBAF in THF (96% yield). Both of these transformations were effected at rt and under essentially neutral conditions (Scheme 2). Furthermore, repetition of this sequence of enamide

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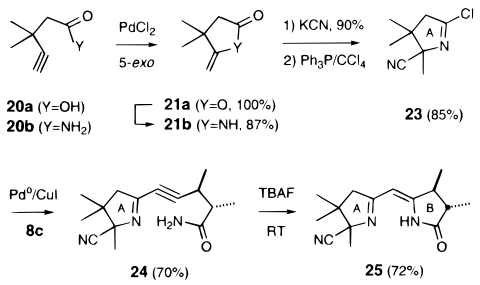
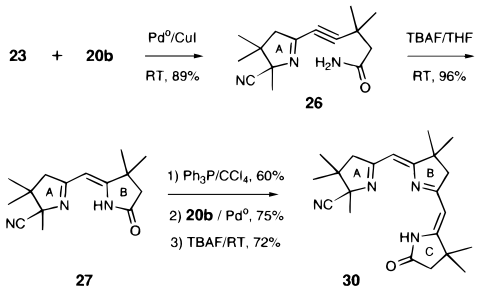
Scheme 1



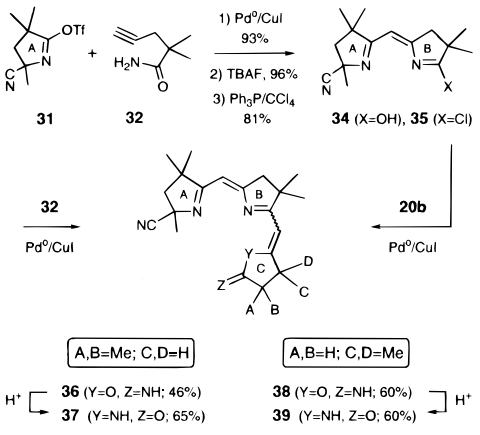
activation (**27** → **28**, Ph_3P/CCl_4), alkyne coupling (**28** → **29**, Pd°, *no CuI*) and cyclization (**29** → **30**, TBAF) led directly to the *Z*,*Z*-tripyrroline **30**, which had identical physical and spectral properties as the material previously reported by Eschenmoser in his model studies for the synthesis of cobyric acid (**6**).[3b,11]

Scheme 2



It was important to explore the effect of adjacent substituents on both the coupling and cyclization steps. Steric crowding turned out not to be a problem, as demonstrated for the case of iminoyl triflate **31** and alkyne amide **32**. Once again, Sonogashira coupling of **31** with **32** afforded an excellent yield of the corresponding pyrrolinoalkyne **33** (not shown, 93%), which underwent cyclization at rt with TBAF to give a 96% yield of the *Z*-semicorrin **34** (X = OH). Chlorination of **34** with Ph_3P/CCl_4 then gave an 81% yield of the iminoyl chloride **35** (X = Cl). Interestingly, Pd(0)-mediated coupling of **35** with the alkyne amide **32** produced a variable product mixture, dependent mainly upon the presence or absence of CuI. With no added CuI, this reaction was sluggish and was accompanied by considerable decomposition. However, *in the presence of CuI*, coupling of **35** with **32** led directly to the iminolactone **36** (Y = O, Z = NH), which was isolated in 46% yield as the *Z*,*Z*-isomer (Scheme 3). This divergence in reaction

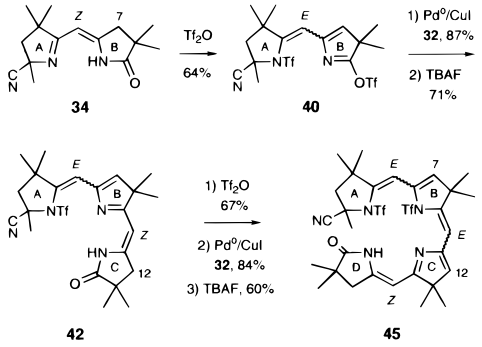
Scheme 3



pathway might be due to complexation of Cu with the A,B-rings of **35**, since concomitant coupling and cyclization of terminal alkynes is not observed with nonchelating substrates (*Note*: CuI was not employed in the coupling of **28** with **20b**, above, which afforded exclusively the alkyne **29**). In any event, acid-catalyzed Dimroth rearrangement of **36** with $TsOH/H_2O/CHCl_3$ then gave a 65% yield of the desired tripyrroline **37** as an inseparable mixture of *E*- and *Z*-isomers.[12] In analogous fashion, Pd(0)/CuI-mediated coupling of semicorrin **35** with the alkyne amide **20b** led directly to the tricyclic iminolactone **38** (60%). As in the case with **36**, iminolactone **38** was cleanly converted to the target tripyrroline **39** upon acid-catalyzed isomerization (60%; *Z*:*E* = 3:1).

Finally, we have evaluated both iminoyl chlorides and triflates as substrates for Pd(0)-mediated coupling. Once in hand, these species generally serve equally well (cf. **31**, above). However, triflate formation is occasionally complicated by competing reaction at nitrogen. For example, treatment of *Z*-semicorrin **34** with Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine led directly to the *N*,*O*-ditriflate derivative **40**, obtained exclusively as the *E*-isomer due to steric repulsion. Interestingly, however, bis-triflation did not forestall subsequent elaboration. Thus, Sonogashira coupling

Scheme 4



of **40** with the acetylenic amide **32**, followed by 5-*exo*-*dig* cyclization, gave an excellent yield of the corresponding tripyrroline **42**, whose *E*,*Z*-geometry was confirmed by X-ray analysis (hydrogen bond between rings B and C).[13] Repetition of this sequence of activation, coupling, and cyclization then afforded the secocorphin derivative **45** (Scheme 4). In **45**, the *E*,*E*,*Z*-geometry derives from hydrogen bonding between rings C and D and steric repulsion between rings A−C.

Complications of the type described in Scheme 4 are unlikely in the cobyric acid (**6**) series, where both the C-7 and C-12 positions bear geminal alkyl groups. Currently we are extending this methodology to the incorporation of meso-substituents, and also to the synthesis of semicorrins having the oxidation state of ring-D in vitamin B_{12}.[14,15]

Acknowledgment. This paper is dedicated to my good friend and mentor, Professor Edward C. Taylor, on the occasion of his 75th birthday.

Supporting Information Available: Copies of ^1H and/or ^{13}C NMR spectra and experimental procedures for compounds **23**−**28**, **30**, **31**, and **33**−**39**, crystallographic data for compound **42** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We are grateful to Professor Doctor Albert Eschenmoser, ETH-Z, for providing us with experimental details and spectral data for several unpublished procedures.

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(13) We are grateful to Dr. Victor G. Young, X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota, for carrying out this analysis (cf. Supporting Information).

(14) Satisfactory analytical and spectral data were obtained for all new compounds reported.

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