Studies on Corrin Synthesis. A Solution to the Introduction of Meso Substituents†

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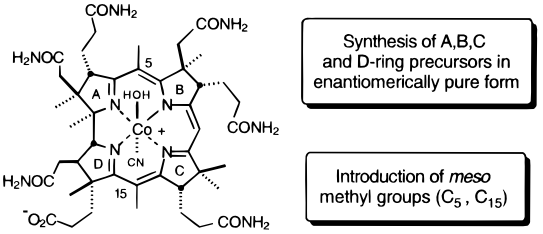
Received December 29, 1998

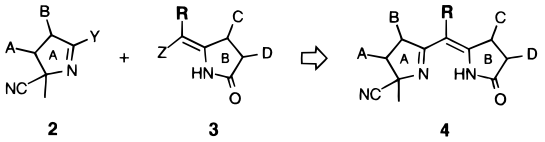
Cobyric acid (**1**) is a member of the corrin class of hydroporphyrins,[1] which incorporate a vinylogous amidine chromophore within a tetrapyrroline skeleton. Members of this class have been the subject of extensive studies, not only because of their biological importance but also due to their intriguing biosynthetic pathway.[2] Recently, this area has seen a resurgence of interest from synthetic chemists.[3,4]



Cobyric Acid (**1**)

Much of this attention derives from the complexity of the corrin nucleus, which can contain up to 10 stereogenic centers about the periphery of the macrocycle.

In most cases the amidine building blocks for corrins are prepared by a combination of iminoether condensations and sulfide contraction steps, both of which were pioneered by Eschenmoser in his extraordinary synthesis of vitamin B_{12}.[5] This methodology can be very effective, as summarized for the hypothetical coupling of lactam derivatives **2** and enamide derivatives **3** to give semicorrins **4**. However, both of these procedures are highly sensitive to steric hindrance, and they are generally unsuited to introducing meso substituents of the type R = alkyl.[6] These last groups are typically added after macrocycle formation, in what is invariably a low-yielding and nonselective step (cf. C_5 and C_{15} in **1**).[2c,6b]

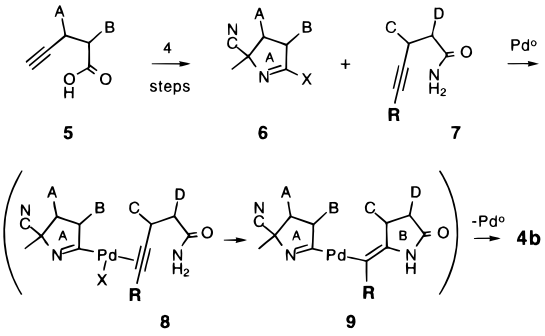


2 **3** **4**

Sulfide Contraction: Y=SH; Z=H, I
Iminoether Condensation: Y=OEt; Z=H, CN

a: R=H; **b**: R=alkyl

Recently, we described an iterative synthesis of semicorrins **4a** (R = H), building upon the facile transformation of pentynoic acids **5** to pyrroline derivatives **6** (X = Cl, OTf).[7a] Pyrrolines **6** were then converted to **4a** by a two-step sequence involving Pd(0)-mediated coupling of **6** with terminal alkyne amides **7a** (R = H), followed by 5-*exo*-*dig* cyclization of the resultant pyrrolinoalkynes (not shown).[7b]



5 **6** **7**

8 **9**

In this paper, we describe our studies with *internal* alkyne amides **7b** (R = alkyl), which cannot undergo direct Sonogashira-like coupling with **6** (i.e., oxidative addition, followed by transmetalization and reductive elimination).[7c] Instead, it seemed plausible that oxidative addition would be followed by π-complexation (**6** → **8**) and then nucleophilic capture to generate vinyl-Pd(II) species of type **9** (Pd ligands are not shown for the sake of clarity). Finally, reductive elimination might lead directly to meso-substituted semicorrins **4b** (R = alkyl), taking advantage of the strong driving force for expulsion of Pd(0) to overcome steric crowding.[8]

Our initial studies were carried out with the alkyne amide **14** (Y = NH_2), which was prepared in straightforward fashion from 1-bromo-2-butyne (**10**) and ethyl isobutyrate (**11**) (cf. Supporting Information). Surprisingly, however, **14** was inert toward Pd(0)-mediated coupling with a variety of iminoyl halides. These included iodopyrrole **15**, which is highly reactive toward Sonogashira coupling with *terminal* alkynes.[7b] Most likely, this failure is due to the relatively weak nucleophilicity of amides in conversions of the type **8** → **9**, above. In contrast, alkyne acid **13** (Y = OH) underwent smooth reaction with iodopyrrole **15**, employing the reagent system $Pd(Ph_3P)_4/BnN(C_2H_5)_3Cl$ with *i*-Pr_2NEt (quaternary ammonium chlorides are essential to this reaction).[8] Under these conditions, we obtained a 99% yield of the meso-substituted lactone **16** (Y = O), which was obtained exclusively as the *Z* isomer (this isomer is stabilized by an

† Dedicated to my good friend and mentor, Professor Edward C. Taylor, on the occasion of his 75th birthday.

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(6) (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. (b) Eschenmoser, A. *Pure Appl. Chem. Suppl.* **1971**, *2*, 69. See also ref 2c.

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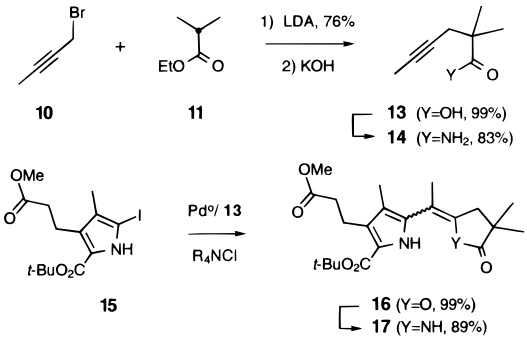
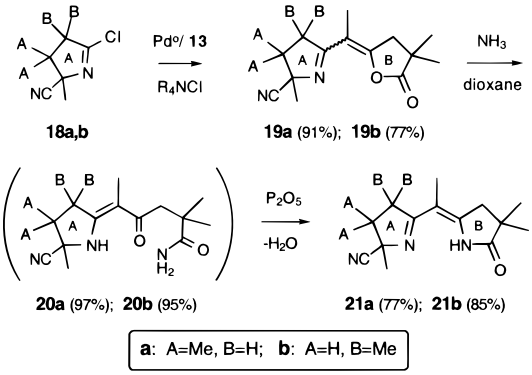
10.1021/jo9824899 CCC: $18.00
Published on Web 02/27/1999



internal hydrogen bond). Finally, brief exposure of **16** to liquid NH_3, followed by dehydration (P_2O_5), gave an 89% overall yield of the desired enamide **17** (Y = NH; *E*:*Z* = 4:5).[7a,9]

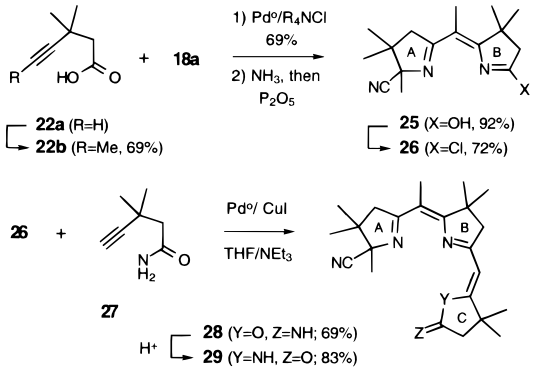
The Pd methodology was readily extended to the synthesis of meso-substituted semicorrins. For example, Pd(0)-mediated coupling of **13** with the iminoyl chloride **18a** (A = Me, B = H) afforded a 91% yield of the enol-lactone **19a**, which was obtained as a 1:1 mixture of *E* and *Z* isomers (GC−MS). In this case, intramolecular hydrogen bonding is not possible, and the *E*:*Z* ratio reflects steric interactions. Ring opening of **19a** with NH_3/dioxane then gave a 97% yield of the ketone amide **20a**, which upon dehydration was cleanly converted to the desired semicorrin **21a** (P_2O_5, 77%). Not



surprisingly, **21a** was obtained exclusively as the *Z* isomer, due to internal hydrogen bonding. In identical fashion, iminoyl chloride **18b** (A = H, B = Me) underwent coupling with **13** to afford a 77% yield of the enol lactone **19b**, which because of strong steric crowding exists predominantly in the *E* configuration (*E*:*Z* = 10:1). Once again, however, aminolysis followed by dehydration provided only the (*Z*)-semicorrin **21b**, in >80% overall yield.

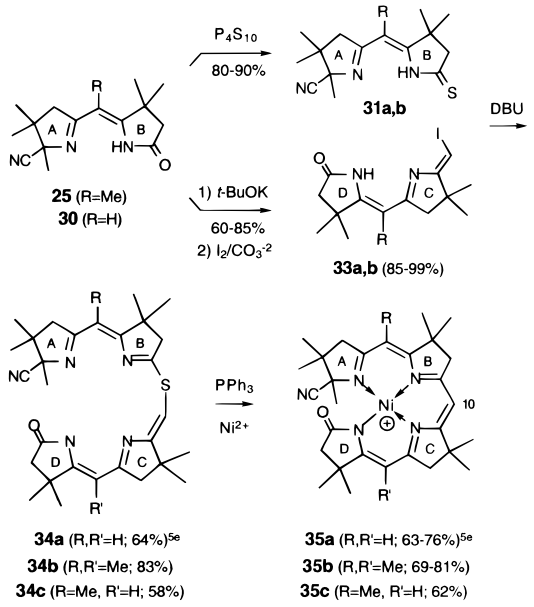
It was important to test the compatibility of this methodology with steric hindrance in ring B, which is a critical issue in the synthesis of semicorrins related to cobyric acid (**1**).[6b] This question was explored using the alkyne acid **22b** (R = Me), which was readily prepared by methylation of **22a** (R = H) using LDA/MeI (69%). We were pleased to find that Pd(0)-mediated coupling of **18a** with **22b** gave a 69% yield of the corresponding enol lactone **23** (analogous to **19a**, above), which upon aminolysis, and subsequent dehydration, afforded semicorrin **25** in 92% yield (lactam tautomer, *Z* isomer only). In comparison, all attempts at preparing **25** employing the sulfide contraction procedure failed (i.e., coupling of thiolactam **2a** [A = Me_2, B = H, Y = SH] with enamide **3a** [C = Me_2, D = H, R = Me, Z = I], see above). Finally, the iterative capability of this strategy was demonstrated by converting **25** to the iminoyl chloride **26** (X = Cl), which was cleanly accomplished using CCl_4/Ph_3P (72%).

(9) See, for example: Micklefield, J.; Mackman, R. L.; Aucken, C. J.; Beckmann, M.; Block, M. H.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc. Chem. Commun* **1993**, 275 and references therein.



Sonogashira coupling of **26** with the alkyne amide **27** then led directly to the iminolactone derivative **28** (69%), via a reaction pathway that most likely involves chelation of Cu.[7a] In any event, acid-catalyzed Dimroth rearrangement of **28** gave an 83% yield of the *Z*,*Z*-tripyrroline **29**,[7a] which is closely related to rings A−C in **1**.

Further iterations of this process are possible, to produce tetrapyrroles and higher analogues.[7a] However, it is sometimes preferable to employ a more convergent approach. Following literature precedent,[5e,f] enamide **25** was converted to semicorrin derivatives **31b** (R = Me) and **33b** (R = Me) and then to vinyl sulfide **34b** by coupling with DBU. Finally,



sulfide contraction of **34b** to secocorphin **35b** was accomplished in 69% yield (81% based on recovered **34b**), following the procedure of Eschenmoser.[5e,f] In this case tetrapyrrole formation is facilitated by metal chelation. We also prepared the mono-meso-substituted secocorphin **35c**, in 62% yield from vinyl sulfide **34c**.[10]

Currently, we are extending this methodology to the synthesis of meso-substituted corrins of type **1**, as well as to chlorins and bacteriochlorins of potential use in PDT. The results of these studies will be reported in future papers.[11]

Supporting Information Available: Copies of ^1H and/or ^{13}C NMR spectra and experimental procedures for compounds **13**, **14**, **16**, **17**, **18b**, **21a**,**b**, **22b**, **23**, **25**, **26**, **29**, **31b**, **32b**, **34b**,**c**, and **35b**,**c**.

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

(11) Financial support of this work by the National Institutes of Health, NIGMS Grant No. GM38913, and the National Science Foundation, Grant No. CHE-9424476, is gratefully acknowledged.