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Synthesis of 1,2,3,7,8,9-Hexahydrodipyrrins and Secocorrins:† Important Precursors for the Construction of Corrins

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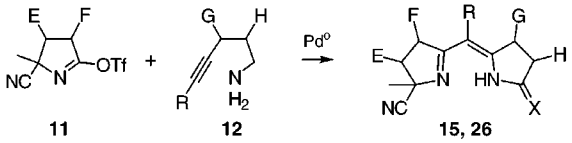
ABSTRACT



Hexahydrodipyrrins 15 (X = H_2) have been prepared by two routes: Pd(0)-initiated coupling/cyclization of triflates 11 and alkyne amines 12 and reduction of semicorrins 26 (X = O).

Tetrapyrroles of the chlorin, bacteriochlorin, and corrin oxidation level serve important functions in nature, and they continue to attract considerable attention.[1] Part of this interest derives from the isolation of novel hydroporphyrins from both marine and microorganisms, some of which have intriguing biological activity.[1,2] In addition, chlorins and bacteriochlorins have potential utility in photodynamic therapy (PDT).[3] The most complex members of this class are the corrins, which can contain up to 10 stereogenic centers on the macrocycle.

In 1977, Eschenmoser et al. published a synthesis of cobyric acid (**6**) that made ingenious use of the recently discovered Woodward−Hoffmann rules.[4a] Thus, rings A−D (**1**−**4**) were coupled employing sulfide contraction methodology to afford the secocorrin derivative **5**, which was maintained in the all-*Z* geometry by complexation with Cd (Figure 1). Secocorrin **5** then underwent a symmetry-allowed, antarafacial 1,16-hydrogen transfer upon exposure to visible light, and the resultant intermediate, upon cycloisomerization, afforded the corrin skeleton of **6** with >95% stereoselectivity. This strategy represents a dramatic improvement over traditional approaches involving coupling of AD + BC ring fragments,[4b] and its implementation was an extraordinary achievement. The versatility of this method is limited only by the availability of complex intermediates of type **1**−**4** and the fact that the sulfide contraction procedure is not well suited for introducing meso substituents.[5] As a consequence, peripheral substituents are generally introduced after macrocycle formation, in what is typically a low-yielding process (cf. the C_5 and C_{15} Me substituents in **6**).[5b] In addition, the lower oxidation state of ring D can present special challenges.

† Nomenclature of Tetrapyrroles (Recommendations 1986). *Pure Appl. Chem.* **1987**, *59*, 779.

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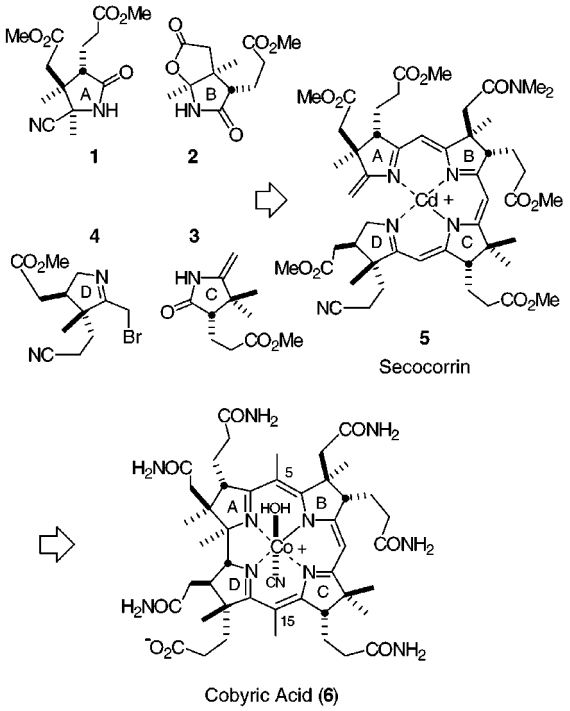


Figure 1. Eschenmoser's cobyric acid synthesis.

Recently, we described an iterative synthesis of secocorphins **9** that took advantage of the ready availability of imidoyl derivatives **7** (X = Tf, Cl) and alkyne acids/amides **8** (R = H, Me; Y = OH, NH_2) (Figure 2).[6a,b] A key step in

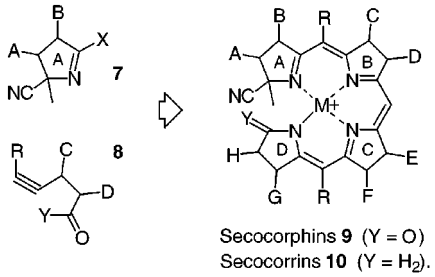
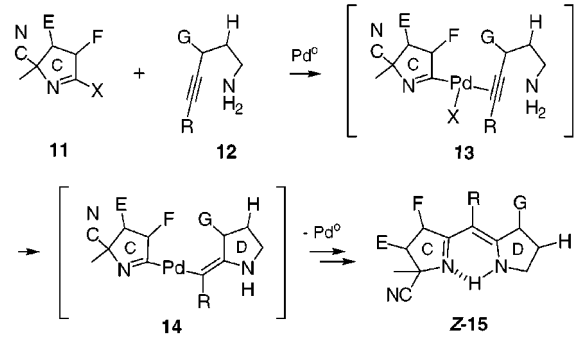


Figure 2. Iterative synthesis of secocorphins **9**.

this synthesis was the Pd(0)-initiated coupling/cyclization of **7** and **8** to afford the corresponding ring AB- and CD-semicorrins. Linking of these fragments employing Eschenmoser's sulfide contraction procedure then gave **9** in good to very good yields (A, C, E, G = Me_2; B, D, F, H = H).[6] The presence or absence of meso substituents at C_5 and C_{15} was dictated solely by the choice of starting alkyne acid/amide **8** (i.e., R = H or Me).

In principle, reduction of ring D in **9** could provide secocorrins **10** having both the proper oxidation state and substitution pattern for cyclization to corrins (cf. also **5** in Figure 1). In practice, however, this transformation is difficult to achieve.[7] As alternate routes to **10**, we have explored two strategies for preparing ring CD-semicorrins where the terminal ring is in the pyrroline oxidation state. Our first approach follows the precedent set in the coupling of imidoyl derivatives **7** and alkyne acids **8** (cf. Figure 2)[6] and takes advantage of the nucleophilic character of alkyne amines **12** in Pd(0)-initiated coupling/cyclization reactions (Scheme 1).[8]

Scheme 1



In this route, oxidative addition of Pd(0) to imidoyl derivatives **11** (X = Tf, Cl) would be followed by π-complexation and then nucleophilic capture to generate vinyl-Pd(II) species of type **14** (Pd ligands are not shown for the sake of clarity). Finally, reductive elimination would afford ring CD amidine derivatives **15** (R = H, alkyl), presumably as the *E* isomers (retention of configuration).[9] However, we expected that (*E*)-**15** would undergo rapid equilibration to the more stable (*Z*)-**15**, which contains an internal hydrogen bond. As previously noted,[6b] the thermodynamic driving force for expulsion of Pd(0) in **14** should overcome any steric crowding in the transition state leading to **15**.

A potential advantage of this approach is the relative mildness of the steps employed. In addition, we expected that chiral alkyne amines of type **12** could be readily derived by reduction of the corresponding amides, which we have previously prepared using a modified Nicholas-Schreiber reaction.[10] In model studies, this reduction was achieved in excellent yield by treatment of alkyne amides **16** with LAH/Et_2O (Scheme 2). Alkyne amines **17a**−**e** were chosen to evaluate the effects of steric hindrance and alkyne substitution pattern on reactivity.

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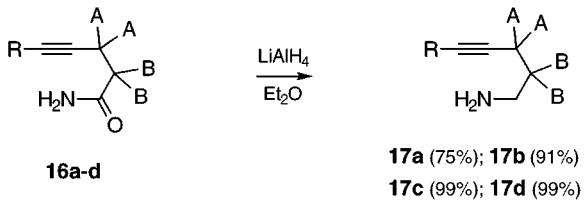
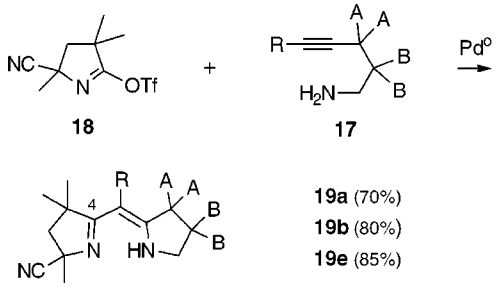
Scheme 2



a: A = H, B,R = Me. **b**: A,R = H; B = Me.
c: A = Me; B,R = H. **d**: A,R = Me; B = H. **e**: A,B,R = H.

Our initial experiments were conducted with the iminoyl triflate **18**, whose synthesis we have previously described (Scheme 3).[6a] In this compound, the geminal methyl groups

Scheme 3

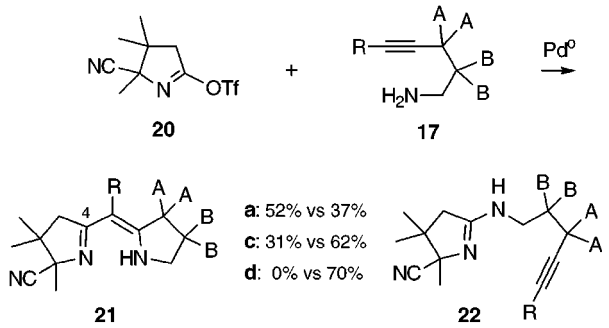


a: A = H; B,R = Me . **b**: A,R = H; B = Me. **e**: A,B,R = H.

at C_3 provide a useful probe of steric hindrance at C_4 (semicorrin numbering). We were pleased to find that Pd(0)-initiated coupling/cyclization of **18** with alkyne amines **17** occurred cleanly and afforded 70−85% yields of the corresponding (H_6)-dipyrrins **19**. For example, **18** combined at room temperature with terminal alkynes **17b** and **17e** (R = H), using the reagent system $Pd(Ph_3P)_4/NEt_3$/THF (80% and 85% yields, respectively). Similarly, reaction of alkyne amine **17a** (R = Me) with **18** gave a 70% yield of the meso-substituted (H_6)-dipyrrin **19a**. This last conversion required warming to 80 °C (MeCN), and was accelerated by added $BnN(Et)_3Cl$ (rate enhancements by ammonium salts have been observed previously).[6b,9] Also, the most effective catalyst was the Pd_2dba_3/TFP system described by Farina.[11] Importantly, the effect of steric hindrance at C_4 on these Pd(0)-initiated reactions appeared to be minimal.

The results obtained with the isomeric iminoyl triflate **20** were less straightforward (Scheme 4). In **20**, the geminal methyl groups at C_2 are well removed from the reacting center (C_4) and, therefore, provide little steric shielding. Consequently, direct nucleophilic displacement at C_4 competes effectively with the Pd(0)-initiated process. In the best case, coupling of **20** with the alkyne amine **17a** gave a 52%

Scheme 4



a: A = H; B,R = Me. **c**: A = Me; B,R = H. **d**: A,R = Me; B = H.

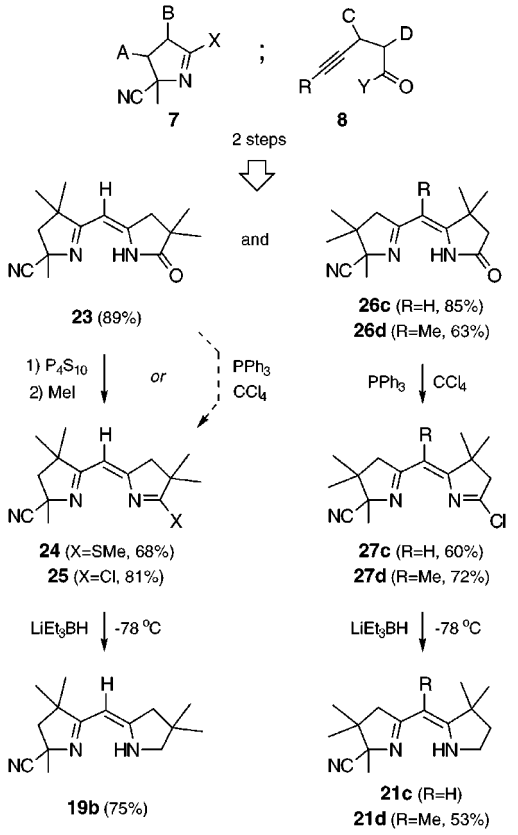
yield of the meso-substituted (H_6)-dipyrrin **21a** (A = H; B, R = Me), accompanied by 37% of amidine **22a**, the product of amine displacement. In analogous fashion, the more sterically hindered alkyne **17c** afforded only 31% of the desired (H_6)-dipyrrin **21c** (A = Me; B, R = H) and 62% of amidine **22c**. Finally, alkyne amine **17b**, which contains the most shielded triple bond (A, R = Me) and the least hindered amine (B = H), gave amidine **22d** as the exclusive product (70% yield). In summary, steric crowding at C_4 has little or no effect on the desired Pd(0)-initiated coupling/cyclization. In fact, it can be beneficial in retarding undesired side reactions. However, shielding of the alkyne bond by both terminal and adjacent methyl substituents has a pronounced effect on selectivity and generally favors direct attack by the amine.

Nucleophilic displacements of the type described in Scheme 4 do not occur with alkyne acids/amides **8**,[6] which are excellent substrates for Pd(0)-initiated coupling and cyclization (Scheme 5). For example, semicorrins **23** and **26c**,**d** were prepared in two steps, and in high yield, from the appropriate imidoyl derivatives **7** and alkyne acid derivatives **8**.[6] In principle, reduction of semicorrin **23** could provide an alternate route to the (H_6)-dipyrrin **19b**, which we had previously synthesized using our coupling/cyclization methodology (cf. Scheme 3). If successful, this approach might then be applied to the synthesis of less accessible (H_6)-dipyrrins of type **21**.

Suprisingly, there appear to be no reports describing the reduction of semicorrins of type **23** to 1,2,3,7,8,9-hexahydrodipyrrins. In any event, this transformation proved to be very challenging. For example, all attempts at the direct reduction of **23** utilizing reagents such as $Et_3OBF_4/NaBH_4$, $BH_3{\cdot}Me_2S/BF_3{\cdot}Et_2O$, LAH, and $LiEt_3BH$ were unsuccessful. In every case, we observed either no reaction or, under more vigorous conditions, severe decomposition. None of the desired **19b** could be detected by TLC analysis.

We also explored the possibility of reducing the thioiminoester **24**, which was readily derived from **23** by initial thiolactam formation (P_4S_{10}; 78%), followed by methylation (MeI/DBU; 87%). In most cases, **24** gave intractable mixtures

Scheme 5

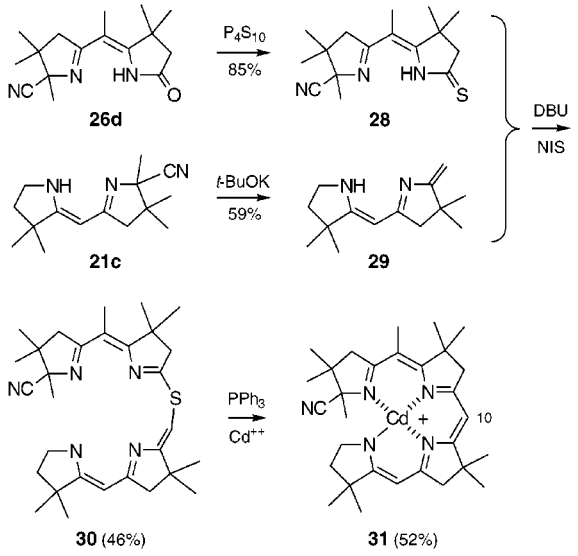


upon attempted reduction.[12a] With $LiBH_4$ in THF, however, we were able to detect trace amounts of **19b** in the crude reaction mixtures. Encouraged by this result, we prepared the more reactive imidoyl chloride **25** (PPh_3/CCl_4; 81%) and tested the same range of reducing agents.[12a] Finally, we were pleased to find that the desired transformation could be effected in 75% yield utilizing Super-Hydride ($LiEt_3BH$) in THF at −78 °C. In identical fashion, **26c**,**d** gave the corresponding imidoyl chlorides **27c**,**d**[6] and **27d** afforded the (H_6)-dipyrrin **21d** (53%).

Having achieved practical syntheses of both semicorrins **26** and (H_6)-dipyrrins **21**, we employed Eschenmoser's methodology to synthesize the meso-substituted secocorrin **31** (Scheme 6).[4b] This required the initial preparation of thiolactam **28** and dipyrrin derivative **29**, both of which were readily obtained following literature precedent (cf. Supporting Information).[4b,6b] Oxidative coupling of **28** with **29** was then accomplished in 46% yield using NIS in the presence of DBU.[2,4b] Finally, treatment of sulfide **30** with PPh_3 and $CdCl_2$ led directly to the secocorrin **31** (52%), which is in the correct oxidation state for photochemical cycloisomerization.[4a,12b]

(12) (a) Reagents: $NaBH_4$, Raney Ni, $NaBH_4/BF_3{\cdot}Et_2O$, $NaBH_4/ZnCl_2$, $Et_3SiH/BF_3{\cdot}Et_2O/NaBH_4$, $LiEt_3BH$, and $LiBH_4$. (b) Satisfactory analytical and spectral data were obtained for all new compounds.

Scheme 6



Following a similar approach to that described above, we believe that this methodology might be extended to the synthesis of cobyric acid (**6**) and other complex, naturally occurring tetrapyrroles. These studies are in progress.

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Supporting Information Available: Copies of ^1H and/or ^{13}C NMR spectra and experimental procedures for compounds **17**, **19**, **20**−**22**, **24**, **30**, and **31**; UV−vis spectra for compound **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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