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Synthesis of Cyclic Enamides by Intramolecular Cyclization of Acetylenic Amides.

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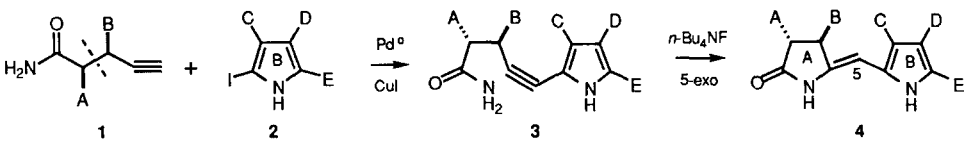
Abstract: Cyclic enamides **12** of a type useful in the synthesis of naturally occurring chlorins, isobacteriochlorins, and corrins have been prepared by a process involving Nicholas-Schreiber condensation to afford acetylenic amides **13**, followed by either *n*-Bu_4NF- or $LiAl(NHBn)_4$-catalyzed ring closure.

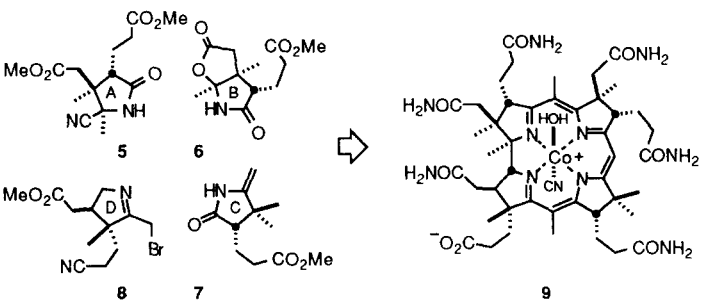
In a recent series of papers we described an efficient synthesis of dihydropyrromethenones of general structure **4**,[1] which were prepared by a two step sequence involving Sonogashira coupling of acetylenic amides **1** with iodopyrroles **2**,[2] followed by fluoride ion catalyzed 5-exo-dig cyclization (Scheme 1). Dihydropyrromethenones **4** are attractive precursors for biologically important linear tetrapyrroles such as phytochrome, phycocyanin, and phycoerythrin.[3] The utility of this approach stems partly from the fact that a wide variety of ring-A synthons **1** (and *ent*-**1**) are available by Nicholas-Schreiber reaction of chiral ester enolates with cobalt stabilized propargylic cations (vide infra, dashed line in **1**, Scheme 1).[1,4] In addition, ring-B pyrroles of type **2** can be prepared on large scale with unequivocal control over regiochemistry.[5]



1 **2** **3** **4**

Scheme 1

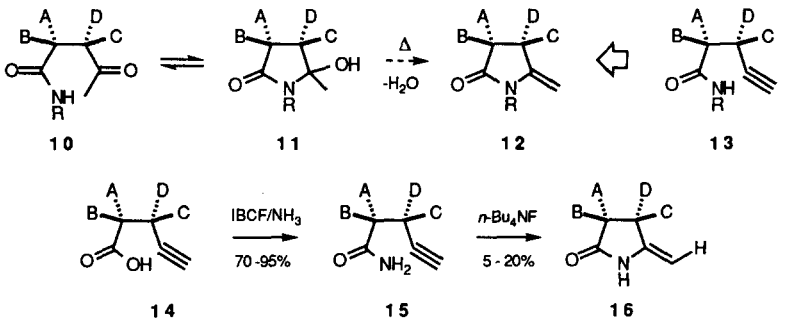
We have been studying the possibility of extending this methodology to the preparation of macrocyclic tetrapyrroles of the chlorin, isobacteriochlorin and corrin oxidation level. Many of these compounds serve important biological functions as vitamins, co-factors, and light absorbing pigments.[6] A landmark synthesis in this area was the preparation of cobyric acid (**9**) by Eschenmoser et al.,[7] who made elegant use of enamide derivatives **5**-**7** and pyrroline **8** for assembling the corrin skeleton (Figure 1). Cobyric acid (**9**) was subsequently converted to vitamin B_{12}, perhaps the most complicated of the naturally occurring corrins. Not surprisingly, highly substituted ring systems of type **5**-**8** present a considerable synthetic challenge.[7]



5 **6** **8** **7** **9**

Figure 1

A variety of strategies have been employed for the synthesis of enamide derivatives of general structure **12**,[8] which can be utilized in either free (cf. **7**), or protected form (cf. **5**,**6**), for constructing macrocyclic tetrapyrroles (Scheme 2; cf. also Figure 1). However, most approaches make use of keto-amide cyclizations of type **10** --> **11**, in which hemiamidal formation is followed by dehydration. This last step frequently requires forcing conditions (T > 150 °C), which can be incompatible with the sensitive nature of **12**. Also, highly substituted keto-amides of type **10** are themselves difficult to prepare, in particular in homochiral form. In this paper we describe an alternative strategy for the synthesis of enamides **12** which involves direct cyclization of acetylenic amides of type **13**. This route has the advantage of proceeding under mild conditions from readily available starting materials,[1] and it has been utilized in an efficient synthesis of a potential ring C precursor of **9**.

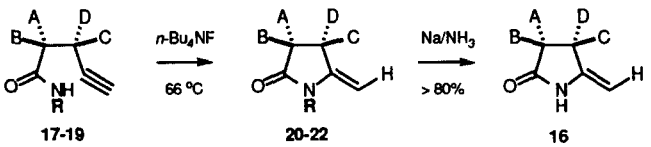


a: A-D = H. **b**: A,B = Me; C,D = H. **c**: A,B = H; C,D = Me.
d: A = H; B,C,D = Me. **e**: A,C = Me; B,D = H. **f**: A,C = H; B,D = Me

Scheme 2

Our initial experiments were carried out with simple N-unsubstituted amides of type **15**, which in the case of **15a-c** were derived in 70-95% yield from the known carboxylic acids **14a-c** using isobutylchloroformate (IBCF) and NH_3 (Scheme 2).[9] Homochiral amides **15e,f**, and racemic amide **15d**, were prepared in excellent overall yield as previously described for acetylenic amides **1** using the Nicholas-Schreiber methodology.[1,4a] Acetylenic amides **15** turned out to be relatively unreactive toward direct cyclization to enamides **16**, affording at best a 10-20% yield of **16d**, and a 5-10% yield of **16c**, upon heating with *n*-Bu_4NF in refluxing THF (65-67 °C, 24-48 h).[1b] Equally discouraging results were obtained with a wide range of reagents which have been successfully employed for the cyclization of related amides,[10] amines,[11] carbamates,[12] and acids.[13] In many cases no reaction was observed at all. Moreover, when cyclization did occur, it often took place with participation of the amide carbonyl group to produce lactones.

Much more satisfactory results were obtained with N-benzyl acetylenic amides of type **17-19** (R = Bn, 4-MeOBN, and 3,4-di-MeOBn), which underwent cyclization to enamides **20-22** at a greatly enhanced rate with *n*-Bu_4NF (TBAF) (Scheme 3, following page). For example, amides **17b-f** (R = Bn) gave essentially quantitative yields of the corresponding enamides **20b-f** upon heating for 3 h with 1.0 eq of TBAF at 66 °C (THF). Even the least reactive member of this series, **17a** (A-D = H), afforded > 50% yields of enamide **20a**. By way of comparison, N-unsubstituted acetylenic amides **15a-f**, which have otherwise identical substituents, afforded at best only trace amounts of enamides **16a-f** after heating 24 h with 6.0 eq TBAF (cf. Scheme 2). Similar rate dependencies on N-substitution pattern have been observed with related amide and carbamate cyclizations.[10d,12] In analogous fashion, benzylamide **18c** (R = 4-MeOBn) gave a 98% yield of enamide **21c**, and benzylamide **19c** (R = 3,4-di-MeOBn) gave 98% of enamide **22c**. Electron rich aromatic rings of the type found in enamides **21,22** have the potential advantage of facilitating N-benzyl cleavage under either oxidative or solvolytic conditions.[14] In any event, enamides **17b-d** gave > 80% yields of the corresponding parent enamides **16** upon reductive cleavage with Na/NH_3 (not optimized).

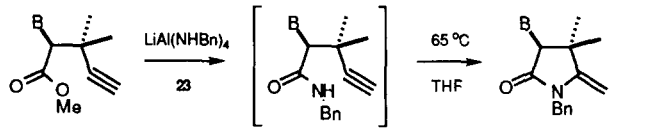


a: A-D = H. **b**: A,B = Me; C,D = H. **c**: A,B = H; C,D = Me.
d: A = H; B,C,D = Me. **e**: A,C = Me; B,D = H. **f**: A,C = H; B,D = Me

Compd (% yield)	**a**	**b**	**c**	**d**	**e**	**f**
17 --> **20** (R=Bn)	50%	98%	98%	94%	92%	93%
18 --> **21** (R=4-MeOBn)	---	82%	98%	94%	---	---
19 --> **22** (R=3,4-di-MeOBn)	---	89%	98%	98%	---	---

Scheme 3

We also tested the activity of several other reagents for catalyzing cyclizations of type **17** --> **20** (R = Bn). As in the case with simple acetylenic amides **15**, no cyclization was observed with benzylamides **17** employing various Pd(II) catalysts under conditions which did not cause concomitant decompositon.[11] In addition, little effect was observed with numerous base catalysts which have previously been employed for related carbamate cyclizations.[12] However, we were interested to find that the reagent system $LiAl(NHBn)_4$ (**23**), prepared in situ from $LiAlH_4$ and $BnNH_2$,[15] was highly effective in promoting cyclization (Scheme 4). Reagent **23** has



24c (B=H)
24d (B=Me)

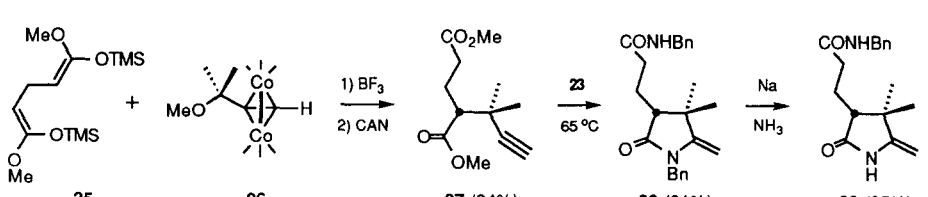
17c (B=H)
17d (B=Me)

20c (B=H) (81%)
20d (B=Me) (71%)

Scheme 4

found considerable utility for the conversion of esters and lactones to benzyl amides,[15] and in the present case it provides a convenient means for the direct transformation of ß-acetylenic esters and/or benzyl amides to cyclic enamides. For example, acetylenic amide **17c** afforded an 81% yield of enamide **20c** after warming for 2 h at 65 °C with 1 molar eq of **23**. In similar fashion, acetylenic ester **24d** gave a 71% yield of enamide **20d** after heating 3 h at 65 °C with 2 molar eq of **23**. It is important to note that no cyclization of intermediate amides **17c,d** was observed in the absence of excess **23**, or with other reagents known to convert esters to amides.[16]

This methodology was also employed in a highly efficient synthesis of a potential ring C precursor for cobyric acid and related corrins (Scheme 5). Thus, condensation of bis-silyl enol ether **25**[17] with cobalt complex **26** afforded a 94% yield of Nicholas adduct **27**,[1,4] which was converted in a single step to benzyl-



25 **26** **27** (94%) **28** (81%) **29** (95%)

Scheme 5

protected enamide **28** by reaction at 65 °C with excess $LiAl(NHBn)_4$ (**23**) (81% yield). Finally, we were pleased to find that the enamide benzyl protecting group in **28** could be selectively cleaved with Na/NH_3, affording the parent enamide **29** in virtually quantitative yield. With suitable modification, we believe that the methodology described in this paper might be applied to the synthesis of a wide range of cyclic enamides in enantiomerically pure form, including those of a type useful for the synthesis of vitamin B_{12} and related materials. This possibility is currently under investigation.[18]

References

1. (a) Jacobi, P. A.; Rajeswari, S. *Tetrahedron Lett.* **1992**, *33*, 6231, (b) *Ibid.* **1992**, *33*, 6235. (c) Jacobi, P. A; DeSimone, R. W. *Tetrahedron Lett.* **1992**, *33*, 6239.
2. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
3. Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024, and references cited therein.
4. (a) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. (b) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163.
5. (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587. (c) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. C* **1971**, 502. See also, (d) Jacobi, P.A.; Cai, G. *Heterocycles* **1993**, *35*, 1103.
6. Flitsch, W. in *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed., Academic Press, Inc.: San Diego, California, 1988; Vol. 43, p.74 (Hydrogenated Porphyrin Derivatives: Hydroporphyrins).
7. Eschenmoser, A.; Wintner, C.E. *Science* **1977**, *196*, 1410, and references cited therein.
8. See, for example (a) Walton, E. *J. Chem. Soc.* **1940**, 439. (b) Schulte, K.E.; Reisch, J. *Arch. Pharm.* **1959**, *292*, 51. (c) Schulte, K.E.; Reisch, J.; Hobl, R. *Arch. Pharm.* **1960**, *293*, 687. (d) Eschenmoser, A.; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 490; *ibid.* **1969**, *8*, 343. (e) Scheffold, R.; Löliger, J.; Blaser, H.; Geisser, P. *Helv. Chim. Acta.* **1975**, *58*, 49. (f) Gossauer, A.; Kuhne, G. *Justus Liebigs Ann. Chem.* **1977**, 664. (g) Cannizarro, L.F.; Grubbs, R.H. *J. Org. Chem.* **1985**, *50*, 2316. (h) Ribo, J.M.; Serra, X. *Monatsh. Chem.***1986**, *117*, 185. (i) Jones, R.C.F.; Begley, M.J.; Peterson, G.E.; Sumaria, S. *J. Chem. Soc, Perkin Trans. I* **1990**, 1959. (j) 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*. See also references 1, 3a, 3e, 5a, 7a, 7b and 8b.
9. (a) Acetylenic acid **17a**: Aldrich Chemical Company, Milwaukee, Wisconsin. (b) Acetylenic acid **17b**: Magnus, P.;.Slater, M.J.; Principe, L.M. *J. Org. Chem.* **1989**, *54*, 5148. (c) Acetylenic acid **17c**: Easton, N.R.; Dillard, R.D. *J. Org. Chem.* **1962**, *27*, 3602. See also, (d) Acetylenic acid **17d**: Crombie, L.; Mackenzie, K. *J. Chem. Soc.* **1958**, 4417.
10. Amide cyclizations: (a) Taylor, E.C.; Katz, A.H.; Salgado-Zamora, H. *Tetrahedron Lett.* **1985**, *26*, 5963. (b) Knapp, S.; Levorse, I. *J. Org. Chem.* **1988**, *53*, 4006. (c) Rudisill, D.E.; Stille, J.K. *J. Org. Chem.* **1989**, *54*, 5856. (d) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. See also references 1 and 8c.
11. Amine cyclizations: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. (b) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812, and references cited therein. (c) McGrane, P.L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459.
12. Carbamate cyclizations: Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4890.
13. Acid cyclizations: (a) Chan, D.M.T.; Marder, T.B.; Milstein, D.; Taylor, N.J. *J. Am. Chem. Soc.* **1987**, *109*, 6385. (b) Marder, T.B.; Chan, D.M.-T.; Fultz, W.C.; Calabrese, J.C.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1885. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B.R. *J. Org. Chem.* **1992**, *57*, 976, and references cited therein.
14. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*; Second Edition, John Wiley & Sons, Inc: New York, 1991.
15. Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.
16. Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815.
17. Wallace, I.H.M.; Chan, T.H. *Tetrahedron* **1983**, *39*, 847.

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