

Enantioselective Syntheses of Ring-C
Precursors of Vit. B₁₂. Reagent Control

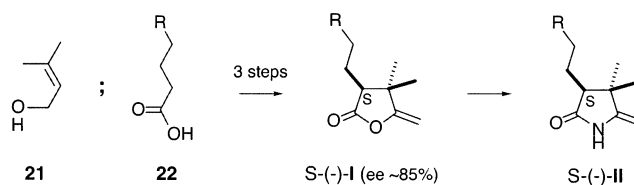
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ABSTRACT



Enactones of the general structure **S(-)-I** were prepared in three steps from alcohol **21** and acids **22** (ee \approx 85%). Lactones **S(-)-I** are versatile precursors to enactams **II** of the type found in Vitamin B₁₂.

In a recent series of papers, we described a general synthesis of semicorrins of type **4**, in which the A- and B-rings were derived from suitably functionalized alkyne acids (Figure 1).¹ Acids **1** were first converted to imidoyl chlorides **2** by a four-step sequence involving (1) Pd(II)-catalyzed cyclization, (2) aminolysis of the resultant enactone followed by cyclodehydration, (3) enamide protection (KCN), and (4) chlorination using CCl₄/PPh₃. Imidoyl chlorides **2** were then transformed to semicorrins **4** by Pd(0)-mediated coupling/cyclization with alkyne acids **3** followed by aminolysis. A

significant advantage to this route is that the coupling of **2** and **3** is relatively insensitive to steric factors, in contrast to more traditional methodology employing thio-Wittig² or sulfide contraction protocols.³ Therefore, meso-substituents **R** can be incorporated directly into the semicorin ring.

Semicorrins **4** are important building blocks for a variety of linear and macrocyclic tetrapyrroles. For example, repetition of the sequence of enamide activation and Pd(0)-mediated coupling–cyclization affords tripyrrolines and higher analogues.^{1a} Alternatively, condensation of **4** with a similarly derived C,D-ring dipyrin provides direct access to seco-corrins **5**,^{1c} which are properly functionalized for photochemical ring closure to produce corrins (Figure 1). Eschenmoser pioneered this route to corrins in his extraordinary synthesis of Vitamin B₁₂.⁴ We are investigating using the alkyne acid methodology for the synthesis of Cobyric Acid (**10**), a known precursor to Vitamin B₁₂ (Figure 2). Our initial objective was to develop enantioselective syntheses of alkyne acids **6–9** or closely related synthons.

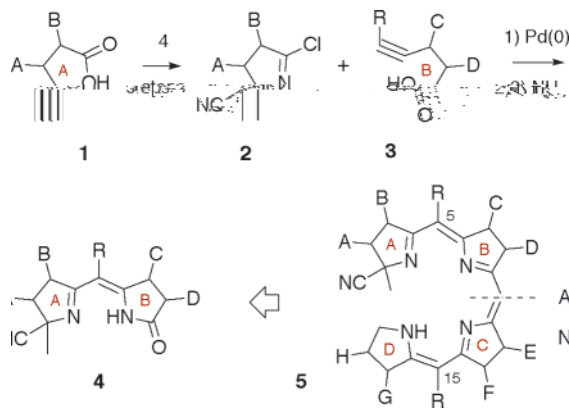


Figure 1. Iterative synthesis of tetrapyrrole derivatives.

(1) (a) Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958. (b) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **1999**, *64*, 1778. (c) Jacobi, P. A.; Liu, H. *Organic Lett.* **1999**, *1*, 341. (d) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **2000**, *65*, 7676.

(2) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079.

(3) (a) Eschenmoser, A. *Pure Appl. Chem. Suppl.* **1971**, *2*, 69. (b) Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 265.

(4) (a) Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410, and references therein.

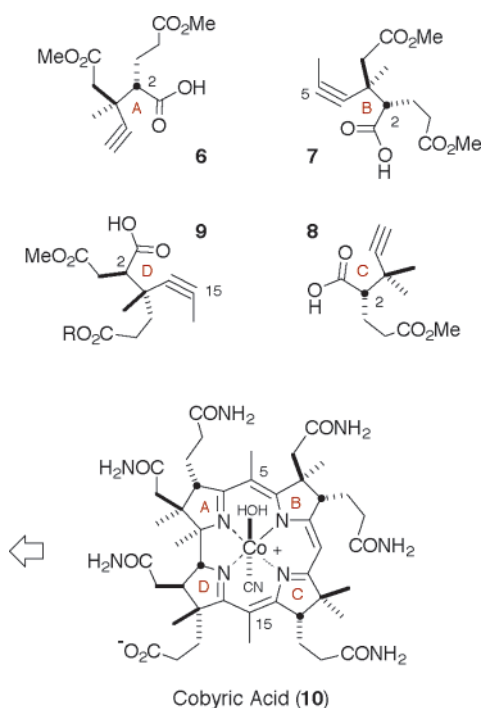


Figure 2. Possible alkyne precursors for Cobyric Acid.

Alkyne acids **6–9** share a number of features in common (Figure 2).⁵ Each has a C-3 quaternary center, and at least one of these substituents is methyl. Also, in **6**, **7**, and **9**, the orientation of the acetate and propionate groups is *syn*. We planned to establish these relationships employing a variant of the Ireland–Claisen rearrangement, a powerful method for synthesizing 1-pentenoic acid derivatives (Figure 3).⁶ In principle, the alkyne oxidation level can be attained by incorporating a leaving group “X” in allylic esters of type **11**. Following 3,3-sigmatropic rearrangement to **13**, elimination of HX would provide the desired alkyne **14**.

The stereochemical outcome depicted in **14** has excellent precedent.⁶ Diastereoselectivity in this transformation is controlled by both enolate and double-bond geometry, with the stipulation that reaction occurs through the most stable chair conformation. As indicated, the desired *syn*-selectivity would be obtained from the (*Z*)-enolate-(*Z*)-alkene configuration of **12**. Control of absolute stereochemistry is also precedented and might be accomplished in one of two ways. When $R \neq H$, C-3 is a chiral center that can be introduced in enantioselective fashion or by alcohol resolution (substrate control).^{6b} Alternatively, with $R = H$, facial selectivity might be achieved using a chiral Lewis Acid ($M^*\text{-Br}$; reagent control). Corey et al. have reported promising results in this area employing the boron reagent **15**.⁷ We have investigated

(5) Acids **6** and **7** are identical except for the C-5 alkyne substituent (H vs Me).

(6) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650. (d) Koch, G.; Janser, P.; Kottirsch, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837, and references therein.

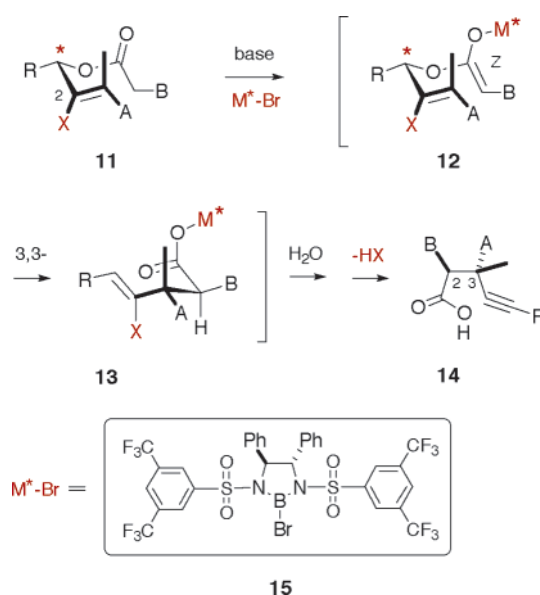
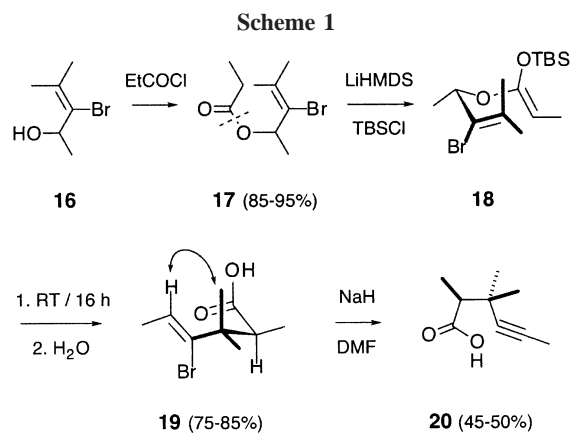


Figure 3. Ester enolate Claisen route to *syn*-alkyne acids.

both of these approaches for controlling absolute stereochemistry in alkyne acids of type **14**. In this Letter we describe our results using reagent control to synthesize ring-C analogues of Vitamin B₁₂.⁸

Our initial experiments were carried out with the model system **17** to test the utility of the Ireland–Claisen rearrangement for preparing alkyne acids (Scheme 1). Racemic



17 was conveniently prepared by propionylation of the allylic alcohol **16** (EtCOCl/pyr), itself derived in ~90% overall yield from mesityl oxide.⁹ We explored a number of procedures for effecting the rearrangement of **17** to **19** under achiral conditions. However, the best results were obtained employing the classic Ireland conditions.^{6a–c} This involved silylation

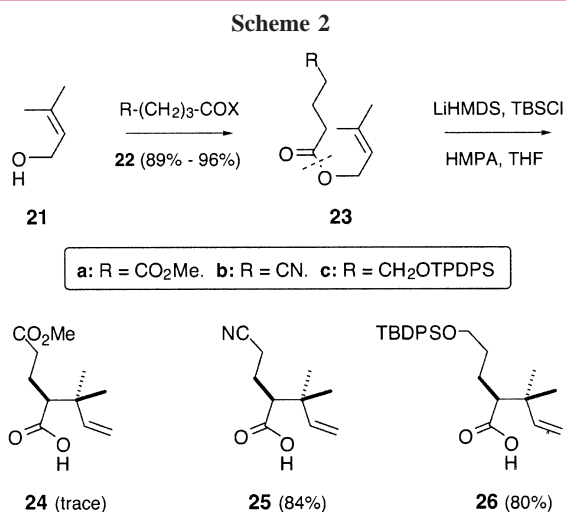
(7) Corey, E. J.; Lee, D. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

(8) Use of substrate control will be described in a following paper.

(9) Mori, H.; Matsuo, T.; Yamashita, K.; Katsumura, S. *Tetrahedron Lett.* **1999**, *40*, 6461.

of **17** at $-78\text{ }^{\circ}\text{C}$ with 1.1 equiv each of LiHMDS/TBSCl, using a solvent combination expected to favor (*Z*)-enolate formation (THF/HMPA). No effort was made to isolate the presumed intermediate **18**, which was cleanly transformed to the (*Z*)-bromoalkene **19** upon warming to room temperature (75–85%).¹⁰ Finally, **19** afforded 45–50% yields of the alkyne acid **20** upon treatment with NaH in DMF (not optimized).

We also tested the compatibility of the achiral Ireland–Claisen rearrangement with sensitive functionality (Scheme 2). Allylic esters **23a–c** were prepared by acylation of the



commercially available alcohol **21** with carboxylic acid derivatives **22a–c** (X = OH, Cl). As with the allylic ester **17** (cf. Scheme 1), **23b** and **23c** gave high yields of alkene acids **25** and **26** using the Ireland protocol. However, ester **23a** presented a special case, since competitive deprotonation occurred at the α -position of the carbomethoxy group. As a result we obtained only trace amounts of the desired alkene **24** under standard conditions. Interestingly, however, similar substrates undergo clean rearrangement utilizing 2.2 equiv of LiHMDS/TBSCl.¹¹

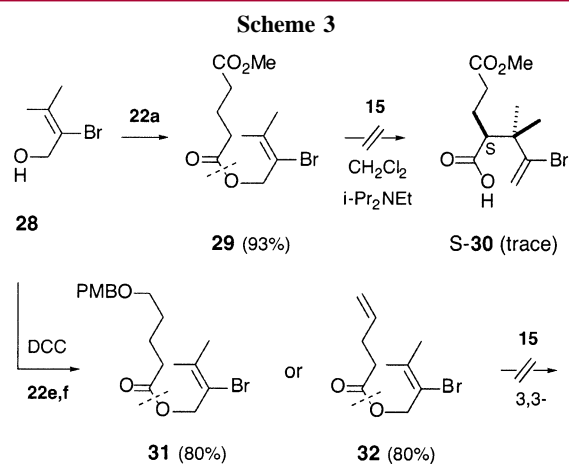
We next studied the reactivity of allylic esters **29**, **31**, and **32** with Lewis acids (Scheme 3). Ester **29** was prepared in 93% yield by condensation of acid chloride **22a** with allylic alcohol **28**, itself derived by bromination of alkene **21**.¹² In analogous fashion, esters **31** and **32** were obtained by DCC-mediated coupling of **28** with the appropriate carboxylic acids **22e,f**. Allylic ester **29** was then reacted with the Corey reagent **15** in an attempt to effect 3,3-sigmatropic rearrangement. Using the literature conditions, we obtained only trace amounts of the desired product *S*-**30** after several days at temperatures from -20 to $0\text{ }^{\circ}\text{C}$.⁷ Similarly, we observed no reaction employing the Oh reagent $(-)\text{-Ipc}_2\text{BCl}$ ¹³ or with achiral reagents such as Bu_2BOTf .

(10) Geometry of **19** was established by NOE studies, which showed a strong interaction between the vinyl C–H and the geminal methyl groups (curved arrow).

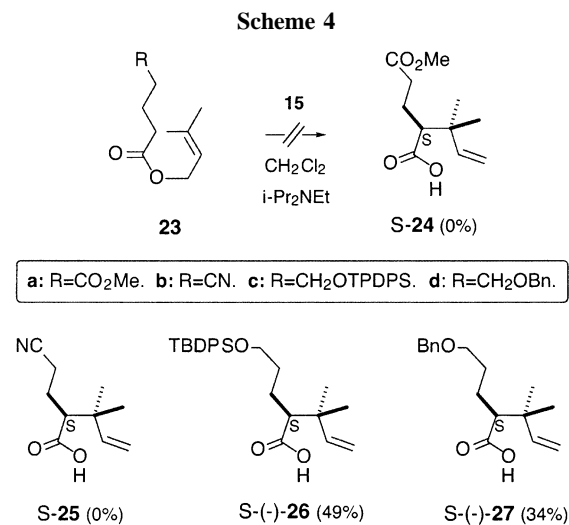
(11) Jacobi, P. A.; Tassa, C. Manuscript in preparation.

(12) Ito, M.; Koyama, T.; Ogura, K. *Chem. Lett.* **1986**, 101.

(13) Oh, T.; Wrobel, Z.; Devine, P. N. *Synlett.* **1992**, 81.



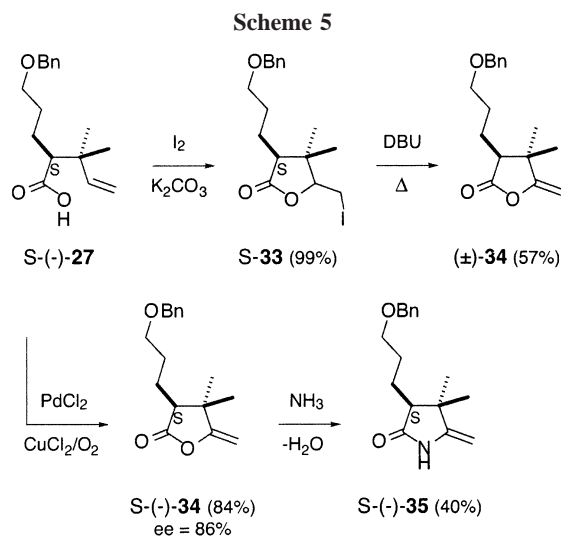
Most likely, the nonreactive nature of **29**, **31**, and **32** stems from a combination of factors. In the case of **29** an important issue is competitive ester enolization, but with **31** and **32**, the principal effects are probably steric. Reagent **15** derives much of its selectivity from its size and structural rigidity,⁷ both of which contribute to steric crowding. These interactions are accentuated during 3,3-sigmatropic rearrangement due to the formation of a quaternary center. Finally, the large bromine atom imparts additional strain into what is already a high-energy transition state, thereby inhibiting reaction. This rationale is supported by experiments carried out with the desbromo substrates **23a–d** (Scheme 4). As with **29**



above (cf. Scheme 3), allylic esters **23a,b** failed to undergo 3,3-sigmatropic rearrangement, presumably due to competing complexation of **15** with the carbomethoxy or nitrile groups. In contrast, substrates **23c,d** were transformed relatively smoothly to the corresponding alkene acids *S*-(-)-**26** and *S*-(-)-**27** with ee $\approx 85\%$.¹⁴ The isolated yields of these materials depended strongly upon the concentration of **15** and reached a maximum of $\sim 50\%$ utilizing a 3-fold excess

(~35% yield with 2.0 equiv **15**). After this point, no further improvement was realized with either additional **15** or longer reaction periods. The reason for this behavior is unclear. These transformations are quite clean with respect to byproduct formation, affording >90% yields of *S*-(-)-**26** and *S*-(-)-**27** based upon recovered **23c,d**.

With reasonable quantities of alkene acids *S*-(-)-**26** and *S*-(-)-**27** in hand, we devoted considerable effort to oxidizing these materials to the corresponding alkynes. These experiments were not fruitful. However, both *S*-(-)-**26** and *S*-(-)-**27** were readily converted to the corresponding enolactones **34** and **36**. With *S*-(-)-**27**, this was initially accomplished by a sequence involving iodolactonization to afford *S*-**33** (99%), followed by base-induced elimination (Scheme 5). Unfortunately, however, dehydroiodination

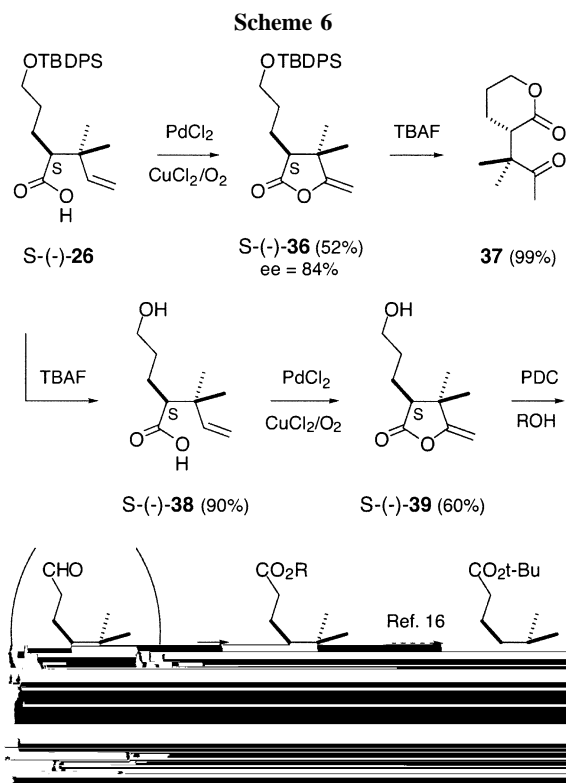


occurred with complete racemization to give (\pm)-**34** in 57% overall yield. Much more satisfactory results were obtained employing the reagent system $\text{PdCl}_2/\text{CuCl}_2/\text{O}_2$,¹⁵ which afforded an 84% yield of *S*-(-)-**34** directly (ee = 86%).¹⁴ Finally, aminolysis of *S*-(-)-**34** and cyclodehydration gave a 40% yield of the enolactam *S*-(-)-**35** (not optimized).¹

In the case of alkene acid *S*-(-)-**26**, oxidative cyclization provided the enolactone *S*-(-)-**36** in 52% yield with ee = 84% (Scheme 6).¹⁴ However, most attempts at removing the TBDPS protecting group gave the rearranged lactone **37**.^{16a} This difficulty was circumvented by carrying out deprotection of *S*-(-)-**26** first (TBAF), which afforded a 90% yield of the alcohol acid *S*-(-)-**38**. Cyclization then took place normally to give the enolactone *S*-(-)-**39** in 60% yield.

(14) Enantiomeric excess (ee) was determined at the enolactone stage employing a Chiralpak AD column (cf. Supporting Information).

(15) Tanaka, M.; Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1986**, *27*, 3165.



Finally, oxidation of *S*-(-)-**39** with PDC/MeOH gave a 70% overall yield of the lactone ester *S*-(-)-**41**.^{16b} This material is in the proper oxidation state for direct conversion to ring-C analogues of Vitamin B₁₂. Alternatively, oxidation of *S*-(-)-**39** with $\text{PDC}/t\text{-BuOH}$ provided the *tert*-butyl ester *S*-(-)-**42** (31%, not optimized),¹⁷ with little or no loss in optical activity. Lactone *S*-(-)-**42** has previously been described by Mulzer et al., who obtained a 90% yield of enolactam *S*-(-)-**43** upon aminolysis/cyclodehydration.¹⁸

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) (a) Modest yields of *S*-(-)-**39** were obtained using pyridine/HF; cf.: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petais, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (b) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235. Oxidation with $\text{PDC}/\text{CH}_2\text{Cl}_2$ gave a 78% yield of the aldehyde *S*-(-)-**40**.

(17) Corey, E. J.; Samuelsson, B. *J. Org. Chem.* **1984**, *49*, 4735.

(18) Mulzer, J.; Riether, D. *Tetrahedron Lett.* **1999**, *40*, 6197.