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Enantioselective Syntheses of Ring-C Precursors of Vit. B_{12}. Reagent Control

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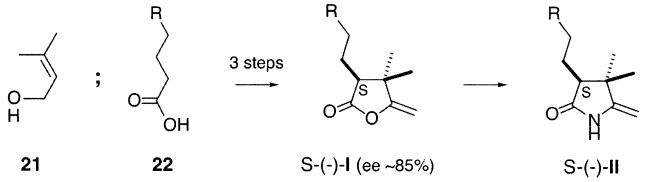
ABSTRACT



Enelactones of the general structure *S*-(–)-I were prepared in three steps from alcohol 21 and acids 22 (ee ≈ 85%). Lactones *S*-(–)-I are versatile precursors to enelactams II of the type found in Vitamin B_{12}.

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 enelactone followed by cyclodehydration, (3) enamide protection (KCN), and (4) chlorination using CCl_4/PPh_3. 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-Wittig[2] or sulfide contraction protocols.[3] Therefore, meso-substituents R can be incorporated directly into the semicorrin ring.

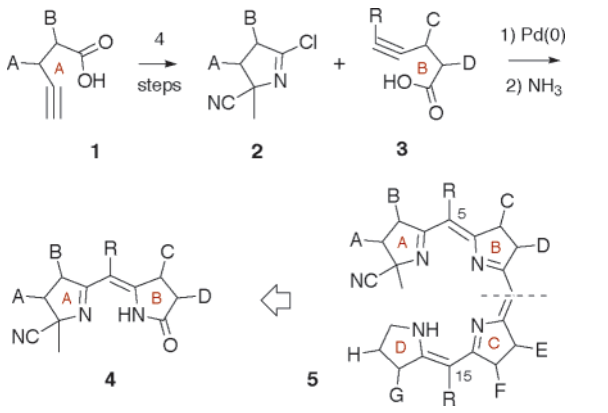


Figure 1. Iterative synthesis of tetrapyrrole derivatives.

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 dipyrrin 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 B_{12}.[4] We are investigating using the alkyne acid methodology for the synthesis of Cobyric Acid (**10**), a known precursor to Vitamin B_{12} (Figure 2). Our initial objective was to develop enantioselective syntheses of alkyne acids **6**−**9** or closely related synthons.

(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.

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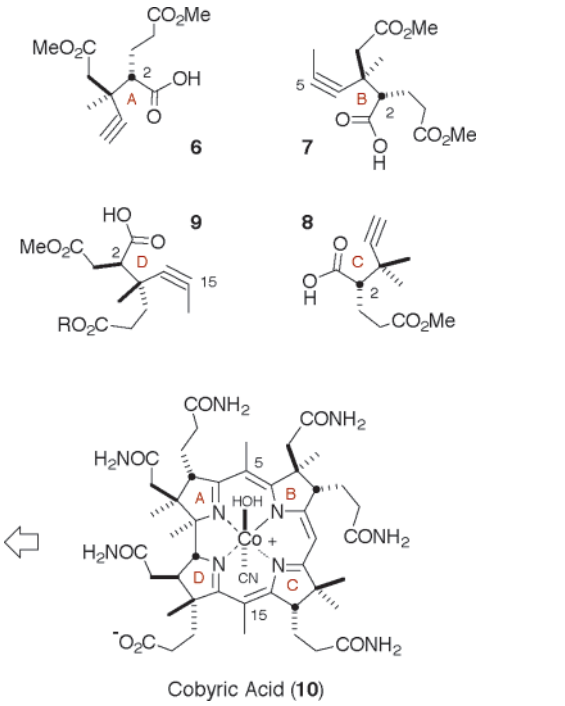


Figure 2. Possible alkyne precursors for Cobyric Acid.

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 ≠ 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*-Br; reagent control). Corey et al. have reported promising results in this area employing the boron reagent **15**.[7] We have investigated

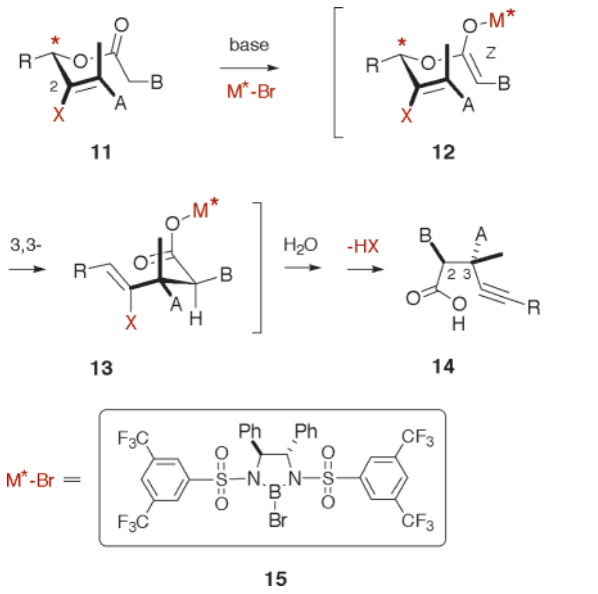
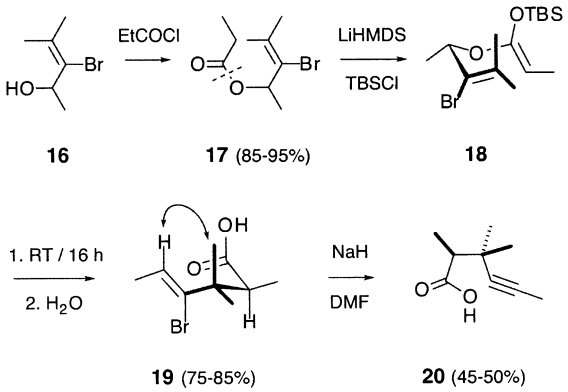


Figure 3. Ester enolate Claisen route to *syn*-alkyne acids.

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 B_{12}.[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

Scheme 1



16 **17** (85-95%) **18**

19 (75-85%) **20** (45-50%)

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

(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.

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

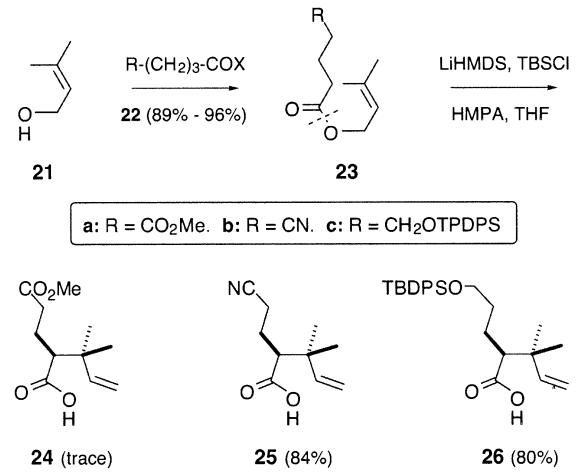
(8) Use of substrate control will be described in a following paper.

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

of **17** at −78 °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

Scheme 2

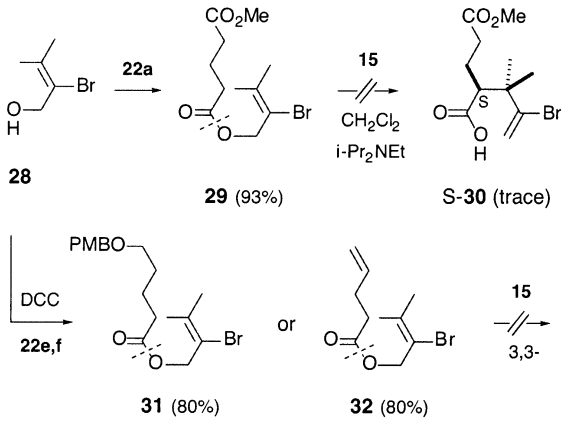


commercially available alcohol **21** with carboxylic acid derivatives **22a**−**c** (X = OH, Cl). As with the allylic ester **17** (cf. Scheme 1), **23b** and **23c** gave high yields of alkene acids **25** and **26** using the Ireland protocol. However, ester **23a** presented a special case, since 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 °C.[7] Similarly, we observed no reaction employing the Oh reagent (−)-Ipc$_2$BCl[13] or with achiral reagents such as Bu$_2$BOTf.

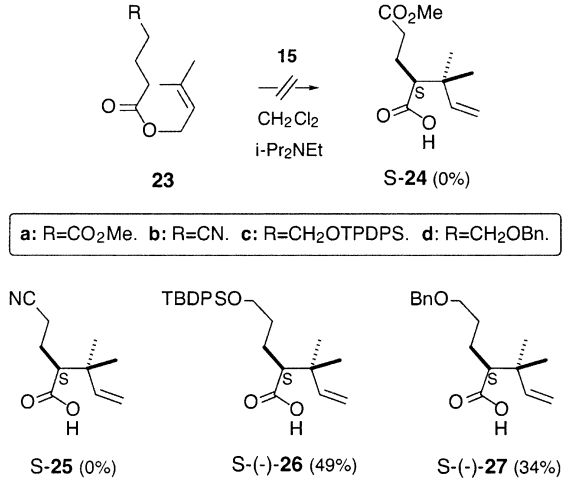
(10) Geometry of **19** was established by NOE studies, which showed a strong interaction between the vinyl C−H and the geminal methyl groups (curved arrow).
(11) Jacobi, P. A.; Tassa, C. Manuscript in preparation.
(12) Ito, M.; Koyama, T.; Ogura, K. *Chem. Lett.* **1986**, 101.
(13) Oh, T.; Wrobel, Z.; Devine, P. N. *Synlett*. **1992**, 81.

Scheme 3



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**

Scheme 4

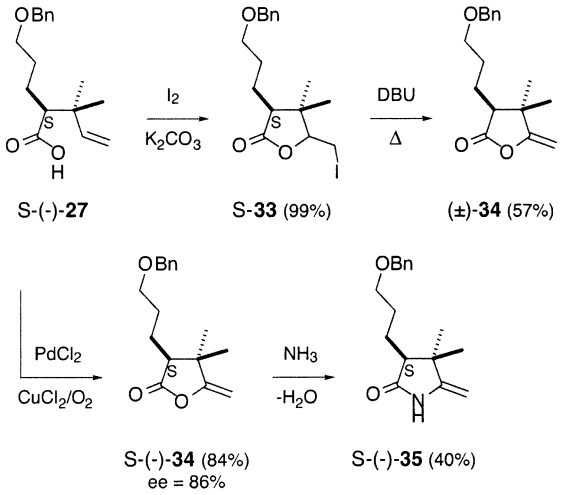


above (cf. Scheme 3), allylic esters **23a**,**b** failed to undergo 3,3-sigmatropic rearrangement, presumably due to competing complexation of **15** with the carbomethoxy or nitrile groups. In contrast, substrates **23c**,**d** were transformed relatively smoothly to the corresponding alkene acids S-(−)-**26** and S-(−)-**27** with ee ≈ 85%.[14] The isolated yields of these materials depended strongly upon the concentration of **15** and reached a maximum of ∼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 enelactones **34** and **36**. With S-(−)-**27**, this was initially accomplished by a sequence involving iodolactonization to afford *S*-**33** (99%), followed by based-induced elimination (Scheme 5). Unfortunately, however, dehydroiodination

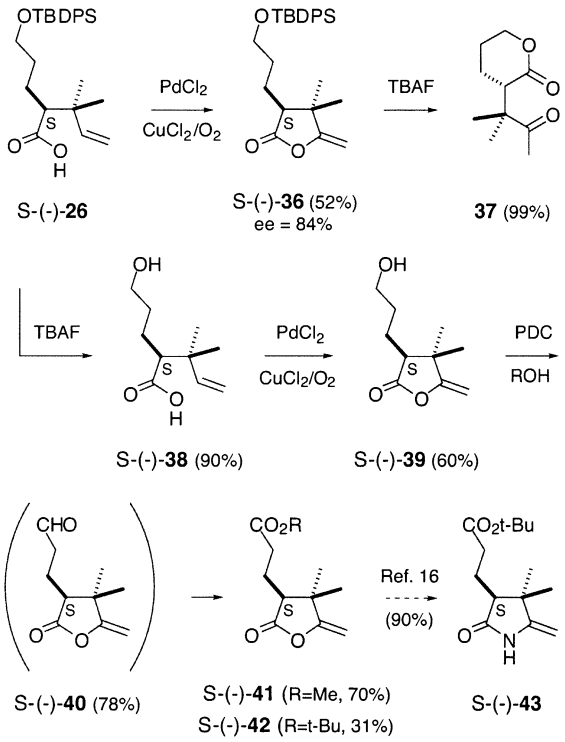
Scheme 5



occurred with complete racemization to give (±)-**34** in 57% overall yield. Much more satisfactory results were obtained employing the reagent system $PdCl_2/CuCl_2/O_2$,[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 enelactam *S*-(−)-**35** (not optimized).[1]

In the case of alkene acid *S*-(−)-**26**, oxidative cyclization provided the enelactone *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 enelactone *S*-(−)-**39** in 60% yield.

Scheme 6



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 B_{12}. Alternatively, oxidation of S−(−)-**39** with PDC/t-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 enelactam *S*-(−)-**43** upon aminolysis/cyclodehydration.[18]

Acknowledgment. Financial support of this work by the National Institutes of Health, NIGMS Grant GM38913, is gratefully acknowledged. We are grateful to Mr. Carlos Tassa of Dartmouth College for carrying out the experiments described in Scheme 1.

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

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

(16) (a) Modest yields of *S*-(−)-**39** were obtained using pyridine/HF; cf.: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (b) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235. Oxidation with PDC/CH_2Cl_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.