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 $\approx$ 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). 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 cyclo-dehydration, (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 or sulfide contraction protocols. Therefore, meso-substituents R can be incorporated directly into the semicorrin 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. Alternatively, condensation of 4 with a similarly derived C,D-ring dipyrrin provides direct access to seco-corrins 5, 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$_{12}$. We are investigating using the alkyne acid methodology for the synthesis of Cobyrinic 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.

Figure 1. Iterative synthesis of tetrapyrrole derivatives.


Alkyne acids \(6-9\) share a number of features in common (Figure 2). 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). 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. 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 preceded 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). 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 \(15.\)

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. 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. 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\(_{12}^*\).

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


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

of 17 at −78 °C with 1.1 equiv each of LiHMDS/TBSCI, 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/TBSCI.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 (−)-Ipc2BCl13 or with achiral reagents such as Bu2BOTf.

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 ≈ 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.

(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).
(~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 base-induced elimination (Scheme 5). Unfortunately, however, dehydroiodination occurred with complete racemization to give (±)-34 in 57% overall yield. Much more satisfactory results were obtained employing the reagent system PdCl₂/CuCl₂/O₂,15 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 TBDDS 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.

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 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

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