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Enantioselective Syntheses of Ring-C Precursors of Vitamin B_{12}. Substrate Control. A Novel Si-Assisted Elimination of Vinyl Bromides

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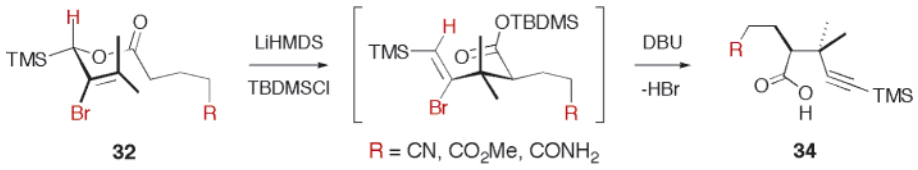
ABSTRACT



Homochiral ring-C precursors 34 of Vitamin B_{12} have been prepared by Ireland–Claisen rearrangement of allyl esters 32, followed by a novel Si-assisted elimination of HBr.

For a synthesis of cobyric acid (**5**) we require access to alkyne acids of type **1**−**4**, which will be employed in an iterative fashion to construct the corrin nucleus (Figure 1, R = CO_2Me, CN, $CONH_2$, etc.).[1] Acids **1**−**4** share a number of features that could facilitate their preparation from a common precursor: each has a C-3 quaternary center, and at least one of these substituents is methyl. Also, in **1**, **2**, and **4**, the orientation of the acetate and propionate groups is *syn* (although in **4** the regio- and absolute stereochemistry are reversed). Finally, acids **1** and **2** are identical except for the C-5 alkyne substituent (H vs Me).

To accomplish these syntheses, we are investigating variants of the Ireland−Claisen rearrangement, a powerful method for synthesizing 4-pentenoic acid derivatives (Figure 2).[2] In principle the alkyne oxidation level found in **1**−**4** can be attained by incorporating a leaving group "X" in allylic esters of type **6** (cf. **7** → **8** → **9**). The desired *syn*-selectivity would be obtained from the *Z*-enolate-*Z*-alkene

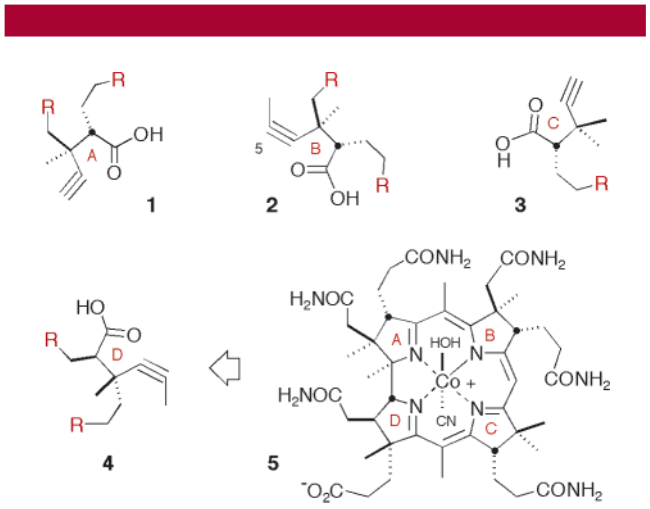


Figure 1. Possible alkyne precursors for cobyric acid (**5**).

configuration of **7**. We planned to control absolute stereochemistry following either of two approaches. With R′ = H, facial selectivity might be achieved by employing a homochiral Lewis acid reagent of type M*-Br (*reagent control*). Corey has reported promising results in this area using a chiral boron reagent.[3] Alternatively, with R′ ≠ H,

(1) For a discussion of this strategy see Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958. Jacobi, P. A.; Liu, H. *J. Org. Chem.* **1999**, *64*, 1778. Jacobi, P. A.; Liu, H. *Org. Lett.* **1999**, *1*, 341.

(2) (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

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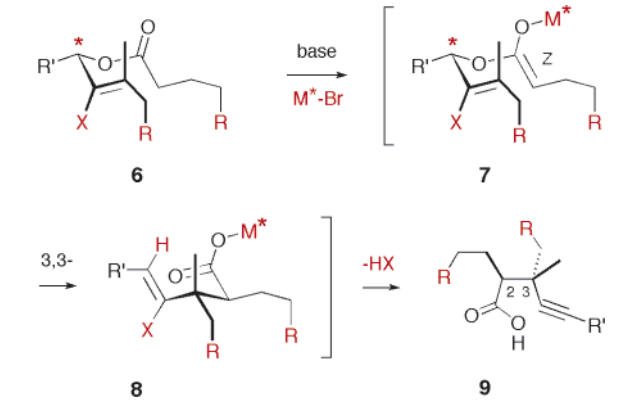
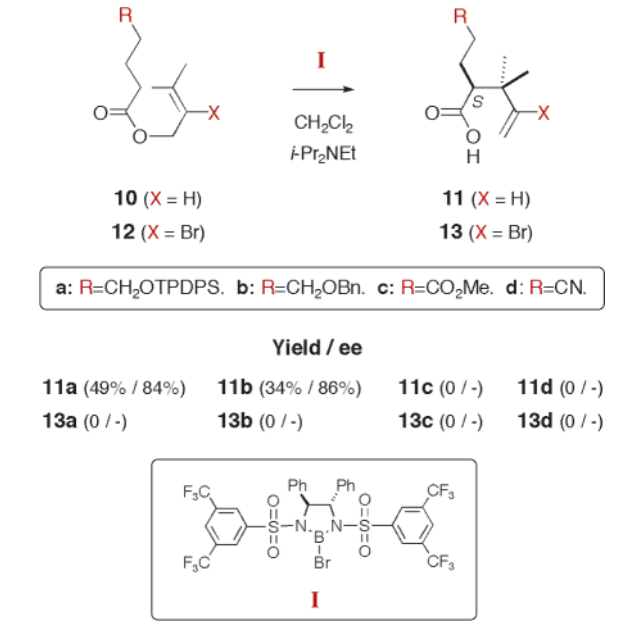


Figure 2. Ester enolate Claisen route to *syn*-alkyne acids.

the starred carbon (*) is a chiral center that might be introduced in enantioselective fashion (*substrate control*).[2b]

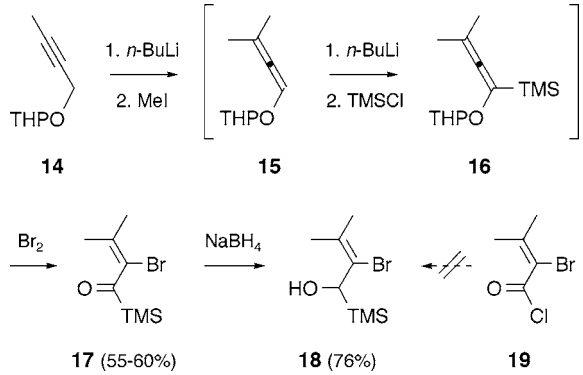
Recently we described preliminary studies employing reagent control to prepare alkyne acids **3** that were partly successful (Scheme 1).[4] A range of allylic esters **10** (X = H) and **12** (X = Br) were subjected to Ireland−Claisen rearrangement employing the Corey reagent **I**.[3] Of the eight substrates examined only **10a** (R = $CH_2OTPDPS$) and **10b** (R = CH_2OBn) gave useful quantities of 4-pentenoic acids, affording **11a,b** in 35−50% yields and ~85% ee. Unfortunately the bromo derivatives **12** were completely unreactive, thereby precluding their use in preparing alkyne acids **3** (cf. Figure 2). This reactivity difference most likely derives from a combination of steric strain and in some cases competing complexation with reagent **I** (i.e., when R = CO_2Me, CN).[4]

Scheme 1



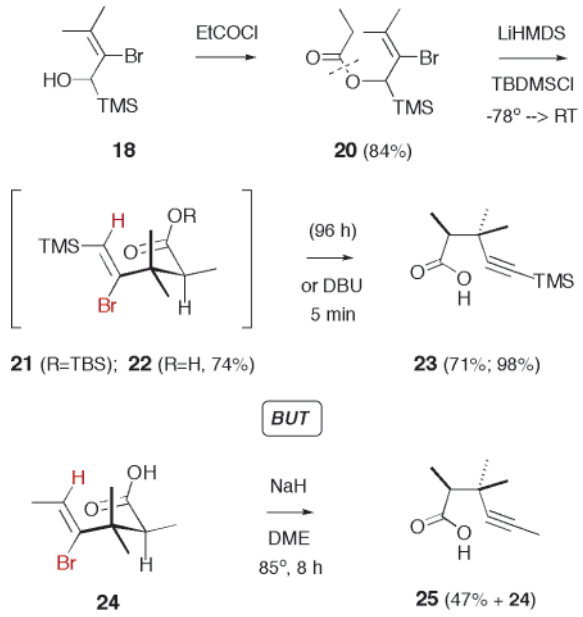
In principle *substrate control* offers a more practical means to control enantioselectivity by avoiding the use of bulky and/or rigid chiral Lewis acids. We investigated this approach beginning with the silyl alcohol **18** (Scheme 2), which is properly constituted for conversion to alkyne acids **3**. In this case the TMS group serves as a proton surrogate to induce chirality (vide supra).[2b] The ketone precursor to **18** was prepared following the general procedure of Reich et al.,[5] involving sequential alkylation of the propargyl alcohol derivative **14** with MeI followed by TMSCl. The resultant allene **16** then gave a 55−60% overall yield of **17** upon addition of bromine (a number of attempts to prepare **17** using the readily available acid chloride **19** failed). For our initial studies this material was reduced with $NaBH_4$, which gave a 76% yield of **18** in racemic form.

Scheme 2



The Ireland−Claisen methodology was first tested with the model system **20** to avoid possible complications from competing enolization (Scheme 3). Following literature precedent,[2] **20** was treated with 1.1 equiv each of LiHMDS and TBDMSCl (*tert*-butyldimethylsilyl chloride) in THF/

Scheme 3



HMPA at −78 °C. Upon warming to room temperature the resultant ketene silyl enolate (not shown) underwent smooth rearrangement, affording a 74% yield of alkene acid **22** after 1 h at 25°. Interestingly, **22** was accompanied by varying amounts of alkyne acid **23**, which increased to 71% after standing 96 h. Alternatively, **23** was obtained in 97% yield upon brief exposure of **22** to DBU (5 min). To better understand this remarkably facile elimination we prepared the alkene acid **24**,[4] which differs from **22** only in the substitution of a CH3-group for TMS. Compound **24** was inert to DBU at room temperature, and elimination of HBr was only partly complete after heating at 85° for 8 h with NaH/DME (47%; 3:1 **25**:**24**). Clearly the TMS group plays an important role in facilitating the conversion of **22** to **23**.

We believe the enhanced reactivity of **22** can be traced to two factors: the structural rigidity imposed by the vinyl bond and the ability of Si to stabilize *both* α-anions (the α-effect) and *β*-cations (the *β*-effect) (Figure 3).[6] For the general case

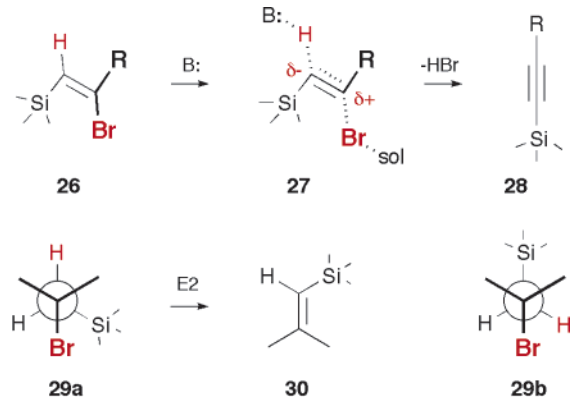
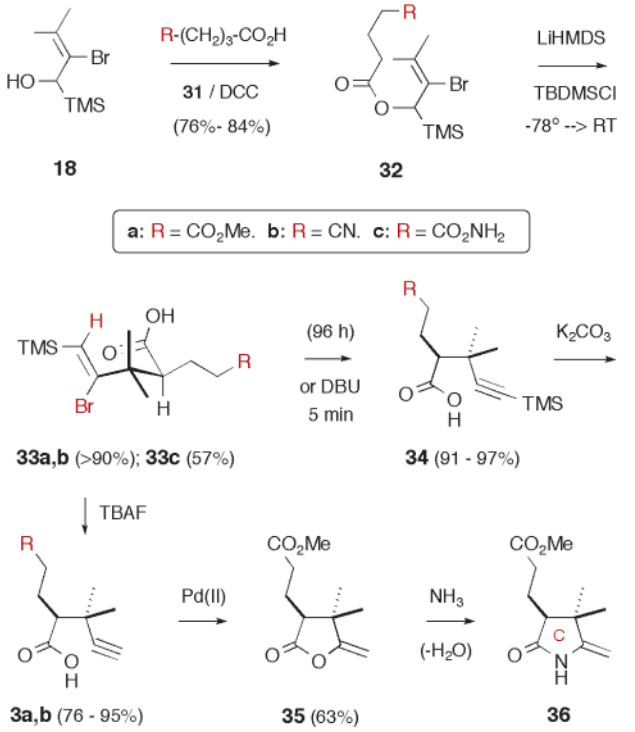


Figure 3. Si-assisted elimination of HBr.

of **26** → **28**, C−H bond cleavage is assisted by "negative hyperconjugation", utilizing the low-lying Si-alkyl *σ**-orbitals to stabilize developing negative charge. Concomitantly, the vinyl-Si bond is held coplanar to the breaking C-Br bond, where the *β*-effect is most pronounced (hyperconjugation). These interactions should significantly stabilize the E2-like transition state **27** leading to *anti*-periplanar elimination of HBr.[7] It is worth noting that simultaneous activation of this type is not feasible for silyl alkyl bromides **29**, since coplanarity of the Br, H, and Si bonds is impossible (cf. conformer **29a**). These species normally react via desilylbromination, which occurs readily from conformation **29b**.[6]

After considerable experimentation these model studies were adapted to the more complex systems necessary to prepare alkyne acids of type **3** (Scheme 4). The starting

Scheme 4



allylic esters **32a**−**c** were prepared in ∼80% yield by DCC coupling of the allylic alcohol **18** with the appropriate carboxylic acids **31a**−**c**. We initially were concerned that competitive enolization might interfere with the desired Ireland−Claisen rearrangement leading from **32** to alkene acids **33**. However, conditions were eventually found that accomplished this transformation in good to excellent yields (cf. Supporting Information). With **32a,b** enolate generation was carried out with premixed TBDMSCl, employing 1.1−2.1 equiv each of TBDMSCl/LiHMDS in THF/HMPA at −78 °C. Upon warming to room temperature the alkene acids **33a,b** were produced in >90% yield. Amide **32c** was a special case requiring 4.1 equiv each of TBDMSCl/LiHMDS. The lower yield of **33c** (57%) was partly due to competing dehydration (i.e., **33c** → **33b**). As above (Scheme 3), the desired alkyne acids **34** were obtained in excellent overall yield either upon standing for 96 h at room temperature or after 5 min with DBU. Desilylation using K_2CO_3/MeOH then afforded the parent alkyne acids **3** (75−95%), which were also obtained directly from **33** upon treatment with TBAF.[8] The structure of **3a** (R = CO_2Me) was confirmed by Pd(II)-induced cyclization to the known enelactone **35**[4] and subsequent aminolysis to afford **36**, the Woodward−Eschenmoser ring-C precursor to cobyric acid (**5**).[9]

To complete the enantioselective syntheses of alkyne acids **3**, it remained to prepare chiral, nonracemic silyl alcohol *S*-**18**. Initially this was accomplished by resolution of (±)-

(3) Corey, E. J.; Lee, D. *J. Am. Chem. Soc.* **1991**, *113*, 4026.
(4) Jacobi, P. A.; Li, Y. *Org. Lett.* **2003**, *5*, 701.
(5) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.
(6) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, NY, 2000.
(7) Computational studies of this reaction are in progress.

(8) This reaction appears to take place by initial Si-assisted dehydrobromination followed by F-induced desilylation. When limited to short reaction periods, mixtures of **34** and **3** were obtained.

18, which gave *S*-**18** of ee >99%.[2b] This material was then carried on to enantiomerically pure *S*-**3a** and *S*-**35** in identical fashion to that described above for racemic **18**. Surprisingly, the enantioselective reduction of trimethylsilyl ketone **17** proved to be problematic, affording only modest ee's with a range of chiral reducing agents (Figure 4). The most

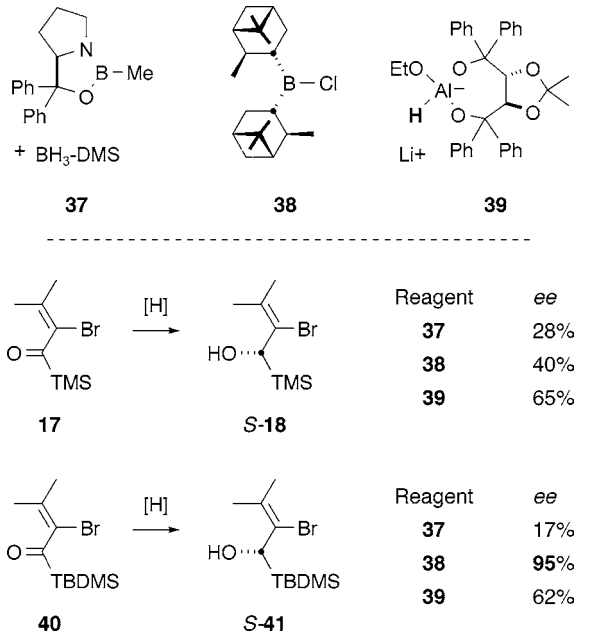
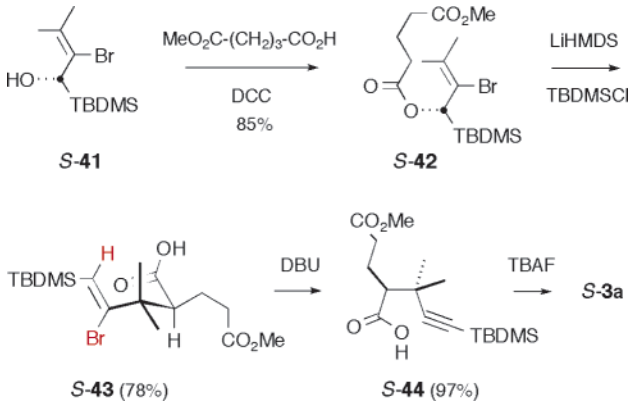


Figure 4. Asymmetric reduction of silyl ketones.

promising of these were (*R*)-2-methyl-CBS-oxazaborolidine/BH_3-DMS (**37**, ee 28%),[10] (+)-*B*-chlorodiisopinocampheylborane (DIP-Cl, **38**, ee 40%),[11] and Seebach's (−)-Taddol-derived reagent **39** (ee 65%).[12] This lack of selectivity may reflect poor steric differentiation between the trimethylsilyl and vinylbromide groups in **17**. In any event, much better results were obtained with the *tert*-butyldimethylsilyl ketone **40**, which provided alcohol S-**41** of ee >95% upon reduction with (+)-DIP-Cl (**38**).[13] Finally, conversion of alcohol S-**41** to alkyne acid S-**3a** was accomplished as described above for S-**18**, affording S-**3a** with ee >95% (Scheme 5).

Scheme 5



Extension of this methodology to the synthesis of alkyne acids **1**, **2**, and **4** and cobyric acid (**5**) is in progress.

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

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(9) (a) Eschenmoser, A.; Winter, C. E. *Science* **1977**, *196*, 1410 and references therein. For a different approach to enelactones related to **35**, see: (b) Mulzer, J.; Riether, D. *Tetrahedron Lett.* **1999**, *40*, 6197. (c) We are grateful to Herr Doktor Professor Johann Mulzer, of the Institut für Organische Chemie, Universität Wien, for providing spectral data for **36**.

(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. See also: (b) Yun, H.; Danishefsky, S. J. *J. Org. Chem.* **2003**, *68*, 4519.

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(12) Seebach, D.; Beck, A. K.; Dahinden, R.; Hoffmann, M.; Kühnle, F. N. M. *Croat. Chem. Acta* **1996**, *69*, 459.

(13) The corresponding triisopropylsilyl ketone underwent reduction too slowly to be of practical value.