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Toward the Synthesis of Cobyric Acid. Enantioselective Syntheses of Completely Differentiated Ring D Synthons

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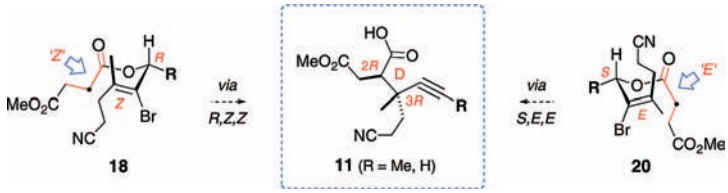
ABSTRACT

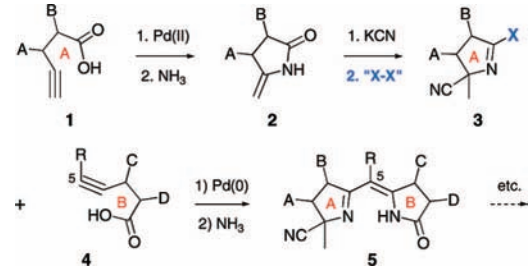


Alkyne acids 11 were prepared in an enantioselective fashion from allylic ester derivatives 18 or 20 by Ireland−Claisen rearrangement, followed by Si-assisted elimination of HBr. The title compounds are attractive ring D synthons for an ongoing synthesis of cobyric acid.

For several years, we have been exploring an iterative synthesis of semicorrins of type **5** and higher homologues, in which the pyrroline and lactam rings are derived from suitably functionalized alkyne acids (Scheme 1).[1] Alkyne acids **1** are first converted to imidoyl chlorides or triflates **3** by a four-step sequence consisting of (1) Pd(II)-catalyzed cyclization; (2) aminolysis of the resultant ene lactone to give lactam **2**; (3) enamide protection (KCN); and (4) lactam activation employing either CCl_4/PPh_3 (X = Cl) or Tf_2O/imidazole (X = OTf). Imidoyl derivatives **3** are then transformed to semicorrins **5** by Pd(0)-mediated coupling-cyclization with alkyne acids **4**, followed by aminolysis (R = H, Me). In an analogous fashion, repetition of this cycle with **5** affords tri- and tetrapyrroline derivatives.[1a] An attractive feature of this approach is that the coupling of **3** and **4** is relatively insensitive to steric factors, in contrast to more traditional methodology employing thio-Wittig[2a] or sulfide contraction protocols.[2b]

Semicorrins **5** are themselves versatile building blocks for a variety of pyrrole-derived natural products. For example, condensation of **5** with a similarly derived C,D-ring dipyrrin provides direct access to *seco*-corrins **6**,[1] which are properly functionalized for photochemical ring closure to produce corrins (Scheme 2). Eschenmoser et al. pioneered this route to corrins in their elegant synthesis of cobyric acid (**7**) and then vitamin B_{12}.[3,4] We are engaged in extending our alkyne acid methodology to the synthesis of **7**, which requires a ready source of homochiral A-D ring synthons **8**−**11**. Linking of these fragments as described above would then afford a fully functionalized *seco*-corrin precursor to **7**, corresponding in structural features to **6**.

Scheme 1. Iteritive Synthesis of Semicorrins and Tripyrrolines



Previously, we described an enantioselective synthesis of the C-ring synthon **10**, a key step of which was an Ireland−Claisen rearrangement of the homochiral allylic ester (*S*)-**12** (Scheme 3).[1b,5]

(1) (a) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **2000**, *65*, 7676, and references therein. (b) Jacobi, P. A.; Tassa, C. *Org. Lett.* **2003**, *5*, 4879.
(2) (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. (b) Eschenmoser, A. *Pure Appl. Chem. Suppl.* **1971**, *2*, 69.

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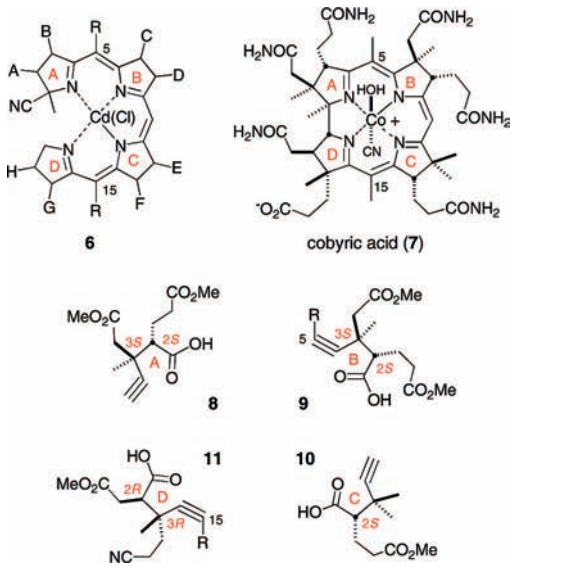
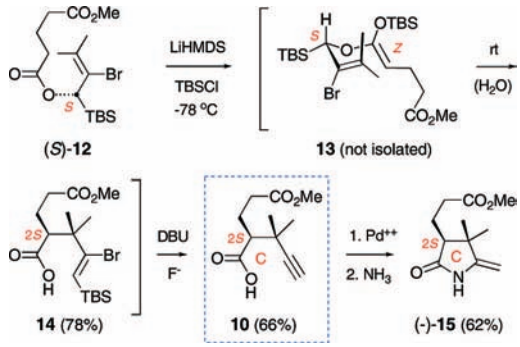
Scheme 2. Alkyne Acid Precursors to Cobyric Acid (**7**)



The *tert*-butyldimethylsilyl (TBS) group in (*S*)-**12** served two roles: (1) as a proton surrogate providing the chirality necessary for inducing the C-2*S* configuration in **10**, and (2) as an anchor for

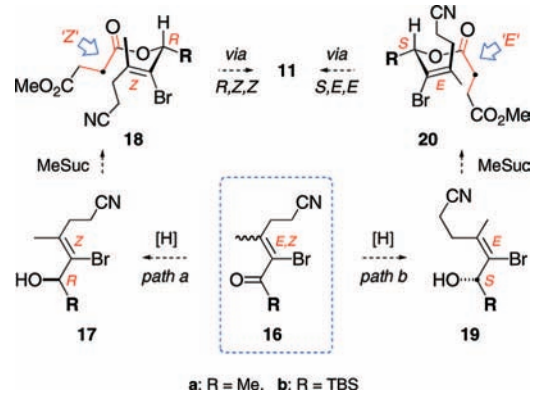
Scheme 3. Ireland−Claisen Route to Ring C (**10**)



stabilizing the desired chair conformation in **13**. As indicated, the combination of (*S*)-configuration in **12** and *Z*-enolate geometry in **13** afforded carboxylic acid **14** in 78% yield and with ee >95%. Alkene **14** was then converted directly to the desired alkyne acid **10** by Si-assisted elimination of HBr,[1b] followed by TBS cleavage. The structure of **10** was confirmed by its two-step conversion to the cyclic enamide (*S*)-(−)-**15**, an intermediate in Eschenmoser's synthesis of **7**.[4] However, while the Ireland−Claisen (I−C) methodology was readily adapted to the synthesis of **10**, its application to ring synthons of type **8**, **9**, and **11** provides a more stringent test. This is especially the case with **11**, which in addition to containing a second, quaternary chiral center (C3), requires differentiation of the three carboxylate functionalities.

In principle, the desired stereo- and regiochemical features in **11** might be introduced employing either of the allylic ester derivatives **18** or **20**, themselves derived in enantioselective fashion from enones **16** (Scheme 4). Thus, following path a, reduction of

Scheme 4. Potential Precursors to Ring D (**11**)



Z-**16** from the *Si* face would afford the homochiral allylic alcohol **17**, which on coupling with methyl succinate (MeSuc) would give **18**. Stereoselective *Z*-silylenolate formation (blue arrow), with in situ I−C rearrangement, would then produce a bromoalkene acid having the 2*R*,3*R*-configuration found in **11** (analogous to **14** in Scheme 3). Alternatively, the identical intermediate could be derived by *Re* face reduction of *E*-**16** (*E*-**16** → **19**), esterification with MeSuc (**19** → **20**), and stereoselective *E*-silylenolate formation (path b). Si-assisted elimination of HBr would then give **11** in four steps starting with **16**.

We planned to synthesize **16** by regioselective cross-coupling of an appropriate organocopper or zinc species with α,β-dibromoenones **22**, themselves derived by Br_2 addition to the corresponding propargyl ketones **21** (Scheme 5). There was evidence that such additions might be stereoselective.[6] However, in the case of **21a** (R = Me),[7a] bromination gave an inseparable ∼1:1 *E*,*Z*-mixture of addition products **22a**, while **21b** (R = TBS)[7b] afforded variable ratios of dibromides *E*- and *Z*-**22b**, depending on the reaction conditions. In neither case could the *E*- and *Z*-isomers be distinguished spectroscopically.

Our initial coupling experiments were carried out with 1:1 *E*,*Z* mixtures of dibromoenone **22a** (R = Me) to test the activity of various combinations of organometallic species and catalysts (Scheme 5). Both isomers proved to be relatively unreactive, requiring much experimentation to develop suitable coupling conditions. Even then, we consistently found that only one isomer of this mixture underwent reaction. Among other examples, the reagent combination of alkyl zinc iodide **23c** (Y = CH_2CO_2Me) and TMSCl/CuCN−2LiCl gave a 43% yield of a single coupling product **16ac**,[8] together with a near-quantitative return of *one* of the isomeric starting materials. This

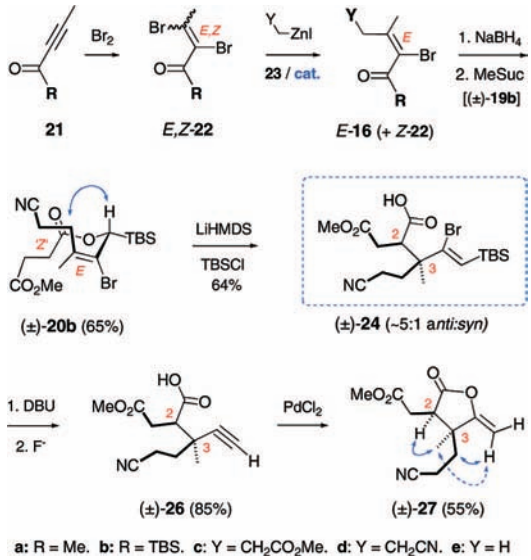
(3) We gratefully acknowledge many stimulating conversations with Professor Eschenmoser on this topic.

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

(5) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650, and references therein.

(6) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

Scheme 5. Preliminary Studies for Synthesizing Ring D



a: R = Me. **b:** R = TBS. **c:** Y = CH_2CO_2Me. **d:** Y = CH_2CN. **e:** Y = H

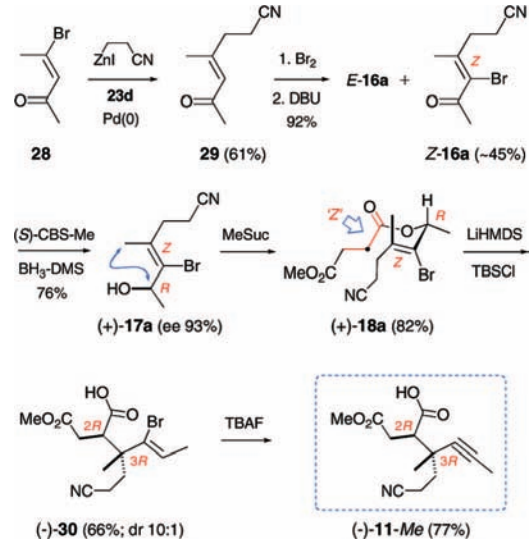
same reactivity pattern held for dibromoenones **22b** (R = TBS) in that only one of these isomers underwent clean cross-coupling with alkylzinc or cuprate reagents. Employing MeCNCuLi, for example, the reactive isomer gave a ~80% yield of the known methylation product **16be** (Y = H).[1b] Also, the reagent combination of alkylzinc iodide **23d** (Y = CH_2CN) and $Pd(OAc)_2/PBu_3$ gave a 79% yield of bromoenone **16bd**,[9] still of unknown geometry.

The stereochemistry of **16bd** could only be determined at a later stage (Scheme 5). Thus, **16bd** was first converted to the I−C precursor (±)-**20b** by $NaBH_4$ reduction to (±)-**19b** followed by esterification with MeSuc. NOE studies on (±)-**20b** then strongly suggested the *E*-configuration as shown (blue arrow). To confirm this assignment, (±)-**20b** was subjected to I−C rearrangement employing the more readily controlled conditions for *Z*-silylenolate formation (LiHMDS/TBSCl in THF/HMPA),[5] which produced a ~5:1 mixture of alkene acids (±)-**24** (64%). The predominate isomer was identified as (±)-**24**-*anti* by its facile conversion to alkyne acid (±)-**26** and then ene lactone (±)-**27**, which was amenable to detailed NOE analysis (blue arrows). Finally, by the same sequence of reactions, the minor product from I−C rearrangement of (±)-**20b** was identified as the desired *syn*-isomer corresponding to (±)-**24**, which on elimination gave alkyne acid (±)-**11**-*H* in Scheme 2.

With the geometry of (±)-**24** now established, and by correlation, that of enones *E*-**16bd** and *E*-**22b**, we set out to reverse the stereochemical outcome of the Ireland−Claisen rearangement leading from (±)-**20b** to (±)-**24**. This was to be accomplished following path b in Scheme 4, requiring stereoselective *E*-silylenolate formation from (±)-**26**. In preliminary studies, however, this transformation was only moderately selective using standard literature conditions,[5] and path b was temporarily put aside. Instead, we opted to devote additional effort to realizing path a in Scheme 4, although we had thus far been unsuccessful in synthesizing the requisite starting materials *Z*-**16**.

To evaluate path a, enone *Z*-**16a** was synthesized by an indirect route, which provided ample material to test the crucial I−C rearrangement (Scheme 6). This synthesis began with the readily

Scheme 6. Enantioselective Synthesis of D-Ring Synthon **11a**



available β-bromoenone **28**,[10] which on Pd-catalyzed coupling with iodozinc reagent **23d** afforded 61−69% yields of the coresponding *E*-enone **29**. Enone **29** was then converted in 92% yield to a mixture of α-bromoenones *E*- and *Z*-**16a**, by a one-pot sequence consisting of bromination followed by dehydrobromination (DBU). Not surprisingly, this procedure gave essentially 1:1 *E*,*Z*-mixtures of **16a**, which, however, were readily separated by chromatography. Each isomer was then reduced separately to the corresponding alcohols (±)-**17a** and (±)-**19a** employing $NaBH_4/CeCl_3$, at which point their geometries were confirmed by NOE analysis (cf. blue arrow in **17a**). We were then pleased to find that enone *Z*-**16a** underwent efficient enantioselective reduction with the reagent system (*S*)-CBS-Me/BH_3-DMS,[11] giving a 76% yield of the chiral alcohol (+)-**17a** (ee 93%). With a ready supply of (+)-**17a** now in hand, the remaining steps leading to the target ring-D precursor **11**-*Me* followed as planned. These involved acylation with MeSuc to give ester (+)-**18a** (82%), followed by stereoselective *Z*-silylenolate formation employing the same conditions as for ester (±)-**20b** in Scheme 5. We thus obtained a ~65% yield of the alkene acid (−)-**30** with dr 10:1. Finally, HBr elimination using TBAF/DMSO produced (−)-**11**-*Me* in 77% yield, completing a six-step synthesis from enone **28**. As with (±)-**26** in Scheme 5, the structure of (−)-**11**-*Me* was corroborated by conversion to the

(7) (a) Hanack, M.; Hassdenteufel, J. R. *Chem. Ber.* **1982**, *115*, 764. (b) Sakaguchi, K.; Fujita, M.; Suzukio, H.; Higashino, M.; Ohfune, Y. *Tetrahedron Lett.* **2000**, *41*, 6589.

(8) (a) Corey, E. J.; Biaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(9) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513.

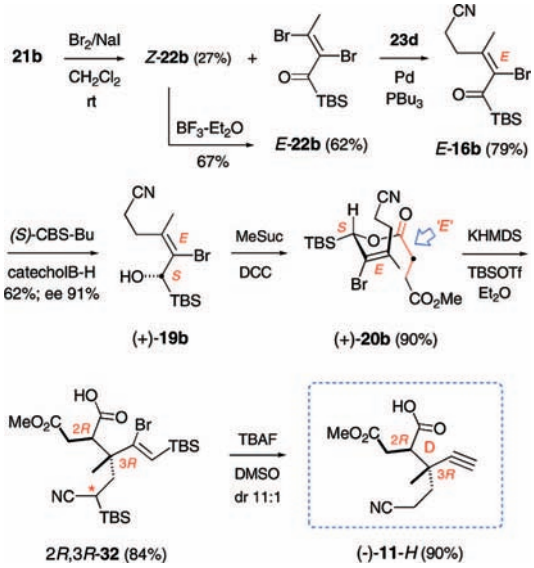
(10) Buono, G. *Synthesis* **1981**, 872.

(11) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986, and references therein.

corresponding ene lactone (+)-**31** (not shown), in this case prepared by CuI-catalyzed ring closure of bromoalkene acid (−)-**30** to avoid competitive 6-membered ring lactone formation.[12a,b]

Following path a, we were routinely able to prepare alkyne acid (−)-**11**-*Me* with high enantio- and diastereoselectivity. However, a number of considerations led us to reexamine the viability of path b in Scheme 4, in particular utilizing dibromides **22b** (R = TBS). One advantage was that isomers *E,Z*-**22b** were readily separable, in contrast to *E,Z*-**22a** (R = Me). Also, we had significantly improved upon the ratio of *Z*-**22b**/*E*-**22b** obtained on bromination (Scheme 7). As originally effected (Br_2, CH_2Cl_2, −78 °C), bromination of **21b** produced a ~3:5 mixture of isomers *E*-and *Z*-**22b**, the unreactive *Z*-isomer predominating.[13] In contrast, on bromination at rt, with catalytc NaI, the desired *E*-isomer was favored by >2:1 (62%:27%). These conditions presumably promote thermodynamic control, since essentially the same product ratio was established on subjecting pure *Z*-**22b** to equilibration with BF_3•Et_2O (67% *E*-**22b**). By this means we were able to conveniently prepare multigram quantities of *E*-**22b** for elaboration to alkyne acid (−)-**11**-*H*.

Scheme 7. Completion of the Synthesis of (−)-**11c**



Pd-catalyzed cross-coupling of *E*-**22b** with alkylzinc reagent **23d** then gave a ~80% yield of *E*-**16b** (Scheme 7). However, the assymmetric reduction of *E*-**16b** proved to be a greater challenge than with the related methyl derivative *Z*-**16a**, likely because of a less definitive "size" difference in the substituents attached to the ketone. Also, the bromoalkene in TBS-ketone *E*-**16b** is probably the "smaller" of the two ketone substituents, a reversal of the ordering found in methyl ketone *Z*-**16a**. Working from this premise, our initial reduction studies on *E*-**16b** were carried out with the same (*S*)-CBS-Me/BH_3-DMS combination employed in the reduction of *Z*-**16a** to *R*-(+)-**17a**, with the expectation that the *S*-enantiomer (+)-**19b** would be favored. This turned out to be the case, as verified by careful inspection of the corresponding Mosher esters.[14] However, the ee for this transformation was only 27%. Following extensive screening, the combination of (*S*)-CBS-Bu and catechol borane was found to give much better results, affording (+)-**19b** in 62% yield and ee 91%.[15] Alcohol (+)-**19b** then gave a 90% yield of allylic ester (+)-**20b** on coupling with MeSuc.

The remaining hurdle to be adressed was in developing reliable conditions for effecting the *E*-silylenolate Ireland−Claisen rearrangement of (+)-**20b**,[16] a transformation that had thus far been problematic (vide supra). However, a solution was found based on the recent studies of McIntosh et al.,[17] who introduced the reagent combination of KHMDS/TIPSOTf in Et_2O (−78 °C). While the TIPSOTf reagent proved too sterically hindered for use with (+)-**20b**, the combination of excess KHMDS/TBSOTf in Et_2O (−78 °C → rt) routinely afforded ~85% yields of rearrangement products 2*R*,3*R*-**32**, incorporating an additional TBS group α to the nitrile (mixture of epimers at C*).[18] This was of little consequence, however, since both silyl groups were cleanly removed on treatment with TBAF in DMSO, giving a 90% yield of ring-D synthon (−)-**11**-*H* with dr 11:1. As with alkyne acids (±)-**26** and (−)-**11**-*Me* above, the structure of (−)-**11**-*H* was corroborated by cyclization to the corresponding ene lactone (+)-**33** (not shown), which was subjected to NOE analysis.

The described six-step route leading from ynone **21b** to alkyne acid (−)-**11**-*H* proceeds with excellent enantio- and diastereoselectivity and provides efficient access to this important ring-D synthon for cobyric acid (**7**). Moreover, we believe that **21b** will serve as a common precursor to each of the remaining ring synthons **8**−**10**.[19]

Acknowledgment. Financial support of this work by the National Institutes of Health, NIGMS Grant No. GM38913, is gratefully acknowledged.

Supporting Information Available: Experimental and NMR spectra for all new compounds, NOE studies, and X-ray crystal structure for (±)-**32** (major epimer). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Modeled on the conditions of Buchwald et al. for amidation of vinyl bromides: (a) Jang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, 5, 3667. (b) In contrast to terminal alkyne acids of type **11**-*H*, internal alkyne acids of type **11**-*Me* give mixtures of 5- and 6-membered ring lactones on cyclization with $PdCl_2$.

(13) The low reactivity of *Z*-**22a** and -**b** is surprising, since numerous examples of selective β-coupling of cyclic α,β-dibromoenones are known. See, for example: Pelphrey, P. M.; Orugunty, R. S.; Helmich, R. J.; Battiste, M. A.; Wright, D. L. *Eur. J. Org. Chem.* **2005**, 4926.

(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512, and references therein.

(15) Corey, E. J.; Bakshi, R. *Tetrahedron Lett.* **1990**, *31*, 611.

(16) These studies were initially carried out with racemic (±)-**20b**.

(17) McFarland, C.; Hutchison, J.; McIntosh, M. C. *Org. Lett.* **2005**, *7*, 3641, and references therein.

(18) The structure of the predominate (*S*)-relative epimer was confirmed by X-ray analysis of a racemic sample (cf. ref 16). We thank the University of Massachusetts Amherst X-ray Structural Characterization Facility (NSF CHE 9974648) for providing diffractometer access and Mr. Travis Benanti of that facility for data collection and refinement.

(19) A reviewer commented that the term "synthon" as originally defined referred to an abstract entity arising from a retrosynthetic analysis (typically a radical, cation or anion). Presently, though, this term is more commonly associated with synthetic precursors or "equivalents".