Published in final edited form as:

Org Lett. 2008 July 3; 10(13): 2837–2840. doi:10.1021/ol800985m.

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

Hui Wang, Carlos Tassa, and Peter A. Jacobi*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire, 03755

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 cobyrinic 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 enolactone to give lactam **2**; (3) enamide protection (KCN); and (4) lactam activation employing either CCl₄/PPh₃ (X = Cl) or Tf₂O/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 dipyrin 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 cobyrinic acid (**7**) and then vitamin B₁₂.^{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**.

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} The *t*-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 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 2-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 *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 *2R,3R*-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 Br₂ 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 = CH₂CO₂Me) 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 same reactivity pattern held for dibromoenones **22b** (R = TBS), in that only one of these isomers underwent clean cross-coupling with alkyl zinc 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 alkyl zinc iodide **23d** (Y = CH₂CN) and Pd(OAc)₂/PBu₃ 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 NaBH₄ 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 enolactone (±)-**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 rearrangement 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 available β -bromoenone **28**,¹⁰ which on Pd-catalyzed coupling with iodozinc reagent **23d** afforded 61-69% yields of the corresponding *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 ($\pm$)-**17a** and ($\pm$)-**19a** employing NaBH₄/CeCl₃, 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/BH₃-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 ($\pm$)-**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 ($\pm$)-**26** in Scheme 5, the structure of (-)-**11-Me** was corroborated by conversion to the corresponding enolactone (+)-**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 diastereo-selectivity. 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 (Br₂, CH₂Cl₂, -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 catalytic 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 BF₃Et₂O (67% *E*-**22b**). By this means we were able to conveniently prepare multigram quantities of *E*-**22b** for elaboration to alkyne acid (-)-**11-H**.

Pd-catalyzed cross-coupling of *E*-**22b** with alkylzinc reagent **23d** then gave a ~80% yield of *E*-**16b** (Scheme 7). However, the asymmetric 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 methylketone **Z-16a**. Working from this premise, our initial reduction studies on *E*-**16b** were carried out with the same (*S*)-CBS-Me/BH₃-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 addressed 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 Et₂O (-78 °C). While the TIPSOTf reagent proved too sterically hindered for use with (+)-**20b**, the combination of excess KHMDS/TBSOTf in Et₂O (-78 °C → rt) routinely afforded ~85% yields of rearrangement products *2R,3R*-**32**, incorporating an additional TBS group alpha 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 enolactone (+)-**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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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

References

1. (a) Jacobi PA, Liu H. J Org Chem 2000;65:7676. [PubMed: 11076634] and references therein. (b) Jacobi PA, Tassa C. Org Lett 2003;5:4879. [PubMed: 14653697]
2. (a) Bishop JE, O'Connell JF, Rapoport H. J Org Chem 1991;56:5079. (b) Eschenmoser A. Pure Appl Chem Suppl 1971;2:69.
3. We gratefully acknowledge many stimulating conversations with Professor Eschenmoser on this topic.
4. Eschenmoser A, Wintner CE. Science 1977;196:1410. [PubMed: 867037]
5. Ireland RE, Wipf P, Armstrong JD III. J Org Chem 1991;56:650. and references therein.
6. Myers AG, Alauddin MM, Fuhry MAM, Dragovich PS, Finney NS, Harrington PM. Tetrahedron Lett 1989;30:6997.
7. (a) Hanack M, Hassdenteufel JR. Chem Ber 1982;115:764. (b) Sakaguchi K, Fujita M, Suzukio H, Higashino M, Ohfuné Y. Tetrahedron Lett 2000;41:6589.
8. Corey EJ, Biaz NW. 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 EJ, Helal CJ. Angew Chem Int Ed 1998;37:1986. and references therein.
12. (a) Modeled on the conditions of Buchwald et al. for amidation of vinyl bromides: Jang L, Job GE, Klapars A, Buchwald SL. Org Lett 2003;5:3667. [PubMed: 14507200]. (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 PdCl₂.
13. The low reactivity of **Z-22a** and **-b** is surprising, since numerous examples of selective β-coupling of cyclic α,β-dibromo-enones are known. See, for example, Pelphrey PM, Oruguntty RS, Helmich RJ, Battiste MA, Wright DL. Eur J Org Chem 2005:4926.
14. Dale JA, Mosher HS. J Am Chem Soc 1973;95:512. and references therein.
15. Corey EJ, Bakshi R. Tetrahedron Lett 1990;31:611.

16. These studies were initially carried out with racemic ($\pm$)-**20b**.
17. McFarland C, Hutchison J, McIntosh MC. *Org Lett* 2005;7:3641. [PubMed: 16092839] 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”.

Scheme 1.

An iterative synthesis of semicorrins and tripyrrolines

Scheme 3.
Ireland-Claisen route to ring C (**10**).

Scheme 4.
Potential precursors to ring D (11).

Scheme 5.
Preliminary studies for synthesizing ring D.

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

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