ORGANIC LETTERS

2012
Vol. 14, No. 17
4698–4700

Asymmetric Catalytic Synthesis of the Proposed Structure of Trocheliophorolide B

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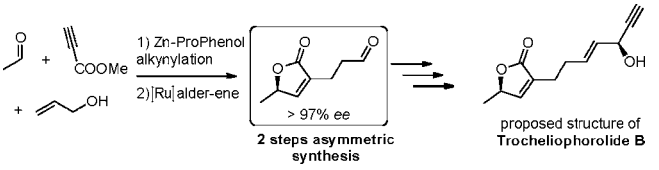
Received July 26, 2012

ABSTRACT

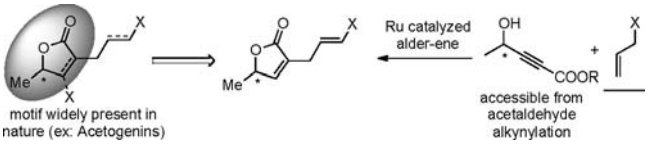


A concise catalytic asymmetric synthesis of the proposed structure of trocheliophorolide B is reported. The synthetic sequence notably features an asymmetric acetaldehyde alkynylation, a Ru-catalyzed alder−ene reaction, and a Zn-ProPhenol ynone aldol condensation. Comparison with the reported data suggests a misassignment of the natural product structure.

Molecules containing the chiral methyl butenolide moiety are widespread in nature (Scheme 1). This particular motif is, for example, found in various biologically active molecules such as in the acetogenin family.[1] Among the strategies to access such compounds, the ruthenium catalyzed alkene−alkyne coupling reaction discovered in our laboratory allows rapid formation of the butenolide skeleton from the corresponding propargylic alcohol and various alkenes (Scheme 1).[2]

In addition to this atom economical redox transformation, our group recently disclosed the Zn-ProPhenol catalyzed alkynylation of acetaldehyde.[3] This reaction provides a particularly efficient and rapid access to a wide range of propargylic alcohols possessing this particular methyl group. Notably, addition of alkynes bearing an electron-withdrawing substituent such as in methyl propiolate gave the best results in terms of yield and enantiocontrol. In these cases, less than 10% of self-aldolization of acetaldehyde were observed together with *ee*'s above 90%.

Scheme 1. Ru Catalyzed Alder−Ene Approach for Rapid Access to Butenolides



With these two particularly attractive methods in hand, we envisaged that their combination would allow the fast and highly enantioselective generation of their common 4-methylbutenolide motif, considerably shortening the access to this class of products. Thus, we were attracted to the implementation of this strategy in the synthesis of a less studied family of natural butenolides isolated in 2001 by the group of Řezanka.[4] These molecules, isolated from the soft corals *Sarcophyton trocheliophorum* and *Lithophyton arboreum* and latter named trocheliophorolides,[5] possess this particular

(1) For reviews on the acetogenins family: (a) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep*. **1996**, *13*, 275. (b) Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem*. **2008**, *4*, doi:10.3762/bjoc.4.48. (c) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E; Cortes, D. *Nat. Prod. Rep*. **2005**, *22*, 269.

(2) (a) Trost, B. M.; Muller, T. J. J. *J. Am. Chem. Soc*. **1994**, *116*, 4985. (b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc*. **1994**, *116*, 7459. (c) Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc*. **1995**, *117*, 1888. (d) Trost, B. M.; Toste, F. D. *Tetrahedron Lett*. **1999**, *40*, 7739. (e) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett*. **2006**, *8*, 5901. (f) Trost, B. M.; Burns, A. C.; Bartlett, M. J.; Tautz, T.; Weiss, A. H. *J. Am. Chem. Soc*. **2012**, *134*, 1474.

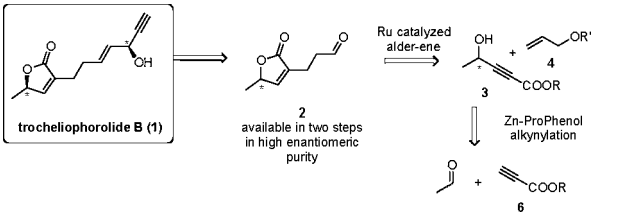
(3) Trost, B. M.; Quintard., A. *Angew. Chem., Int. Ed*. **2012**, *51*, 6704.

(4) For the isolation: (a) Řezanka, T.; Dembitsky, V. M. *Tetrahedron* **2001**, *57*, 8743. In 2011 another group published the synthesis of the proposed structure of Trocheliophorolide D but found some differences in the spectra, suggesting a misassignment of the structure of this member of the family: (b) Hwang, S.; Kim, J. H.; Kim, H. S.; Kim, S. *Eur. J. Org. Chem*. **2011**, 7414.

10.1021/ol302074h
Published on Web 08/22/2012

methyl-butenolide skeleton (Scheme 2). In addition, they exhibit both antibacterial activity against Gram-positive bacteria and toxicity in the brine shrimp bioassay. This bioactivity together with the particular structural framework and the poor number of synthetic studies[4,5] prompted us to undertake the synthesis of trocheliophorolide B. Our retrosynthetic plan (Scheme 2) was devised around the use of the sequential Zn-ProPhenol acetaldehyde alkynylation followed by Ru alkene−alkyne coupling. Final insertion of the remaining stereocenter was first envisaged via another Zn-ProPhenol alkynylation on the corresponding homologated enal.[6]

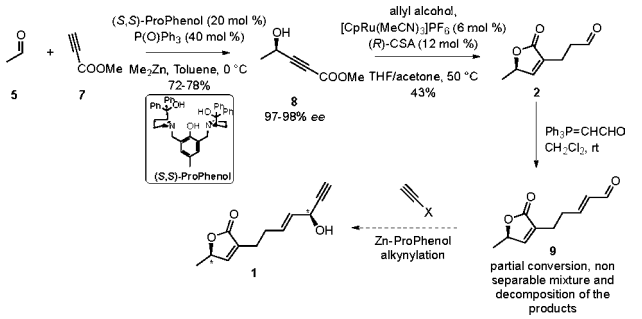
Scheme 2. . Retrosynthetic Analysis of Trocheliophorolide B (**1**)



Scheme 3 depicts our first generation approach. Application of the Zn-ProPhenol asymmetric addition of methyl propiolate to acetaldehyde cleanly provided **8** in 72−78% yield and typically 98% *ee*. The reaction could be run reproducibly on up to the 5 mmol scale allowing a convenient access to this almost enantiopure compound. Application of **8** in the $[CpRu(MeCN)_3]PF_6$ catalyzed coupling with allyl alcohol[2e,f] directly installed both the butenolide skeleton by in situ transesterification and the aldehyde by tautomerization of the initially formed enol creating **2** in 43% yield (Scheme 3).[7] All the attempts at increasing the yield of this transformation failed.[8] In this process, the desired butenolide is obtained as the major product together with approximately 15% to 20% of the butenolide regioisomers and other impurities. However, despite the modest yield obtained, the considerable synthetic shortcut provided by this step still provides a fast and efficient access to **2**. For example, for a synthesis of the acetogenin 4-deoxygiganterin, a 12 step process to prepare the enantiomer of butenolide **2** was employed.[9] Use of penta-2,4-dien-1-ol instead of allyl alcohol in order to directly obtain the homologated enal only gave traces of the product.

Homologation of the obtained aldehyde proved even more challenging. Applying a classical Wittig type homologation using (triphenylphosphoranylidene) acetaldehyde did not give a satisfying yield of **9** (Scheme 3). All the

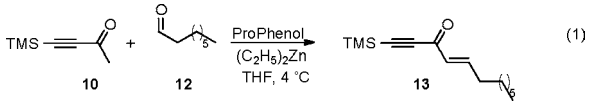
Scheme 3. Initial Attempted Route to Trocheliophorolide B (**1**)



attempts to optimize the reaction (higher temperature, use of benzene, equivalents of nucleophile) only gave partial conversion and poor mass recovery.[8] Forcing conditions only led to decomposition of the products. In addition, a preliminary attempt at Zn-Prophenol catalyzed alkynylation on the obtained mixture of aldehydes only gave a moderate result.[10]

This failure led us to change our strategy and turn our attention to an unprecedented 3-butyn-2-one (**10**) addition−elimination on aldehyde **2** (Scheme 4).[11] This highly constructive step should build, in one single transformation, the appropriate skeleton of the final product. However, such an aldol condensation under catalytic conditions has not been reported.

Using the addition of 4-trimethysilyl-3-butyn-2-one (**10**) as the donor and octanal as the acceptor (eq 1),



different amine catalyzed aldol additions/condensations were examined without success.[12] This failure presumably derives from the strong electrophilic character of the ynone toward Michael additions wherein such amines behave as nucleophiles. Fortunately, turning to the Zn-ProPhenol system promoted the smooth addition of the TMS-protected ynone **10**. Most importantly, the water elimination product could be directly obtained just by increasing the Et_2Zn amount to 50%. In this manner the aldol condensation product with *n*-octanal was obtained in 69% yield. This process proceeded equally well with aldehyde **2** (Scheme 4) to give the desired enone **11** in 64% yield. Both enantiopure and racemic ProPhenol worked equally well. Considering the relatively low pK_a of a butenolide compared to a ketone,[13] thanks to the mild conditions developed, the stereointegrity of the

(5) Spencer, W. T., III. PhD Thesis, Rochester Institute of Technology, Rochester, NY, 2008.

(6) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8.

(7) This result is comparable with results previously obtained (52−55% yield) in the alkyne−alkene coupling using allyl alcohol in ref 2e, 2f.

(8) See Supporting Information for details.

(9) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998**, *54*, 6329.

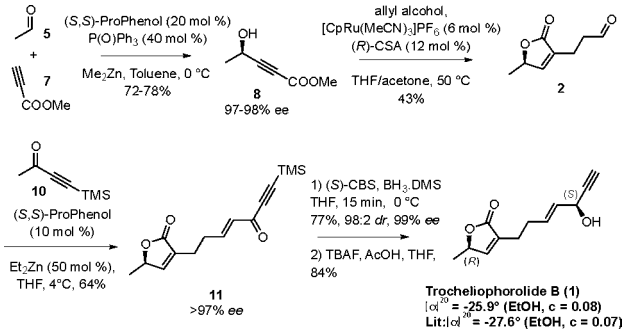
(10) Starting from a 4:1 mixture of enal/aliphatic aldehyde only gave a disappointing 50% conversion.

(11) For relatively limited examples of direct catalytic aldolization of aldehydes by ynones, see: (a) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. (b) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 17111. (c) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417.

(12) Aminocatalysts tested: proline, piperdine, benzylamine, valine.

stereocenter was completely preserved in this reaction (*ee* >97%). Directly employing the nonprotected terminal alkyne considerably decreased the conversion in this reaction to 58% as a 1:1 mixture of the product of simple addition and that of subsequent dehydration.

Scheme 4. Synthesis of Trocheliophorolide B (**1**)



CBS (Corey–Bakshi–Shibata) reduction of the ene–yne–one motif provided the corresponding alcohol with excellent stereopurity (98:2 *dr*, 99% *ee*).[14] Final deprotection of the alkyne failed under classical basic conditions (K_2CO_3, MeOH) leading to the decomposition of the starting material. Fortunately, the use of buffered TBAF provided access to the final product **1** (Scheme 4). To confidently assign the structure of the natural product, both diastereoisomers of **1** (4-(*R*),9-(*S*) and 4-(*S*),9-(*S*)) were prepared with equal efficiency thanks to this modular, stereocontrolled route, starting from either (*R*)-**8** or (*S*)-**8**.

Optical rotation of the (4-(*R*),9-(*S*)) stereoisomer of **1** closely matched the literature data ($[\alpha]^{20}_D = -25.9°$ (EtOH, $c = 0.08$); Lit: $[\alpha]^{20}_D = -27.6°$ (EtOH, $c = 0.07$)). The optical rotation value of the other diastereoisomer (*S*, *S*) ($[\alpha]^{20}_D = +61.9$ (EtOH, $c = 0.10$)) was considerably far from the reported value, suggesting the (4-(*R*),9-(*S*)) stereochemistry of the natural product.

However, NMR analysis of the synthetic product **1** revealed some differences from the NMR data of the isolation report (Figure 1). Notably, in the synthetic samples (in $CDCl_3$), peaks for the aliphatic CH_2 shifted upfield in ^{1}H NMR and downfield in ^{13}C NMR. These differences can be attributed to the fact that the conditions of NMR analysis (solvent, type of spectrometer) were not reported in the isolation paper. Changing the nature of the deuterated solvent considerably shifted the aliphatic CH_2 peaks, but we were not able to find conditions where all peaks correctly matched.[8] Given the observed data for the synthetic sample and the fact that **2** is an already known compound, we are confident of the assigned structure of the synthetic material. This suggests a misassignment of the natural product structure.

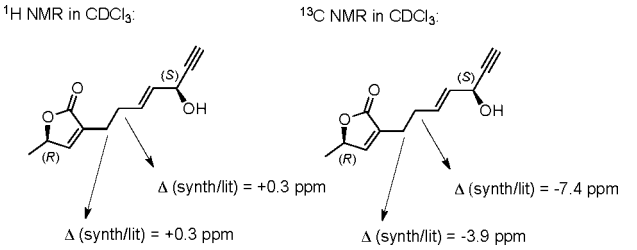


Figure 1. NMR data comparison between synthetic and natural sample.

In conclusion, the proposed structure of trocheliophorolide B could be accessed thanks to a concise five-step catalytic asymmetric strategy. The key steps feature successive acetaldehyde alkynylation/Ru alkene–alkyne coupling and an unprecedented ynone catalytic cross-aldol condensation. Given the impressive synthetic shortcuts, we believe that the strategy used in this study will find broad applications in the synthesis of other complex natural products.

Acknowledgment. We thank the National Science Foundation (CHE-0846427) and the National Institutes of Health (GM-33049) for their generous support of our programs. A.Q. is grateful to the Swiss National Foundation for a fellowship.

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

The authors declare no competing financial interest.

(13) Cf. pK_a = 17.7 for non-substituted butenolide; see: Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319.

(14) For examples of CBS reduction of ene–yne–one, see: (a) Garcia, J.; Lopez, M.; Romeu, J. *Synlett* **1999**, *4*, 429. (b) Garcia, J.; Lopez, M.; Romeu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2617. (c) Tamura, S.; Ohno, T; Hattori, Y.; Murakami, N. *Tetrahedron Lett.* **2010**, *51*, 1523. (d) Sui, B.; Yeh, A.-H.; Curran, D. P. *J. Org. Chem.* **2010**, *75*, 2942. (e) Evans, D. A.; Kværnø, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 16296.