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Advances in Lewis Acid Controlled Carbon–Carbon Bond-Forming Reactions Enable a Concise and Convergent Total Synthesis of Bullatacin

Hongda Zhao, Jeffrey S. T. Gorman, and Brian L. Pagenkopf*

The Department of Chemistry, The University of Western Ontario, London, ON N6A 5B7, Canada, and The Department of Chemistry, University of Texas, Austin, Texas 78712

bpagenko@uwo.ca

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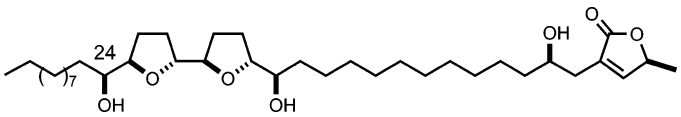
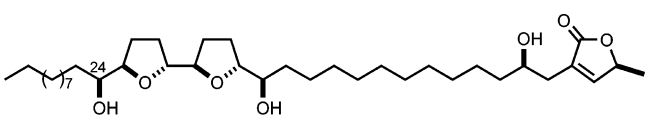
ABSTRACT



Lewis acids control regioselectivity in the alkylation of *epi*-chlorohydrin and the stereochemistry of an alkyne addition to set the C24/C23 anti relationship. These advances facilitate an efficient total synthesis of bullatacin in 13.3% overall yield from commercial starting materials.

Bullatacin is an archetypal member of the family of annonaceous acetogenin natural products that have been extensively studied for both the synthetic challenges their structures elicit and the potent and selective cytotoxicity these compounds display.[1] The bis(THF) region with its flanking hydroxyl groups is found in various stereochemical arrangements in related natural products, and the ubiquitous butenolide portion occurs in natural products of even greater number and variety.[2]

Bullatacin has been synthesized previously,[3] but we found that for purposes of analogue preparation more operationally simple, cost-effective, and modular pathways were desired. We imagined a straightforward, scaleable approach involving three key retrosynthetic disconnections. The first is introduction of the butenolide in as complete a state as possible to enhance synthetic convergence. The second is addition of a hydrocarbon chain critical to our analogue project. This segment will serve as a spacer that will allow correlation of activity on the distance between the THF region and the butenolide moiety.[4] Finally, introduction of the left-hand aliphatic chain to a desymmetrized 2,5-bis(THF) completes the strategy. In practice, however, two of these tasks proved to be overtly inefficient: establishing the C(23)−C(24) anti stereochemistry by addition of the left-



1, Bullatacin

Figure 1. Bullatacin

(1) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.

(2) (a) Bermejo, A.; Figadère, B.; Zafra-Polo M. C.; Barrachina, I.; Estornell E.: Cortes D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (b) Zafra-Polo M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117.

(3) (a) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245−4248. (b) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035−6051. (c) Sinha, S. C.; Sinha, B. A.; Yazbak. A.; Keinan E. *Tetrahedron Lett.* **1995**, *36*, 9257−9260. (d) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419−4427. (e) Hoye, T. R.; Tan, L. S. *Tetrahedron Lett.* **1995**, *36*, 1981−1984.

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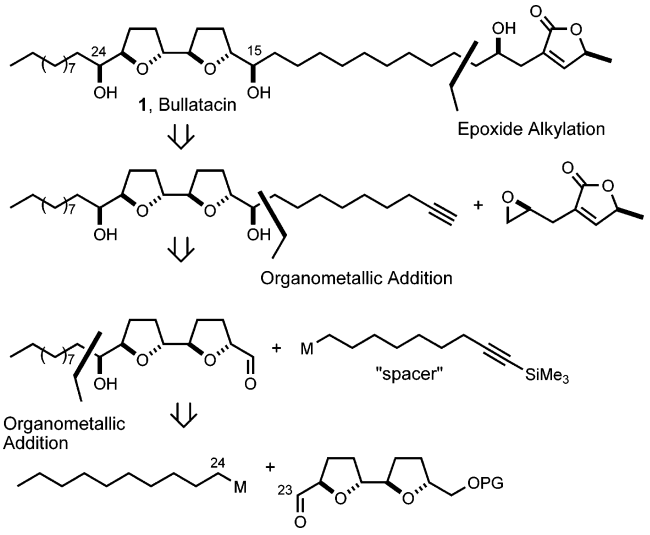
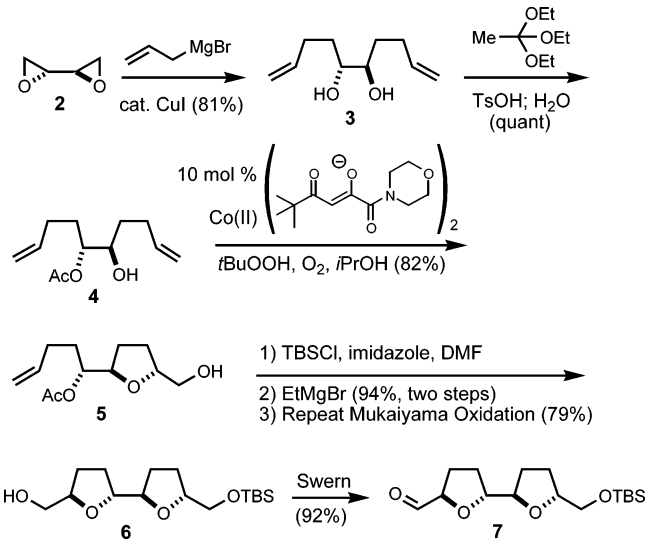
Scheme 1. Retrosynthetic Analysis



Scheme 2. Preparation of the Desymmetrized Bis(THF) Core Segment



hand aliphatic chain to a C(23) aldehyde and preparation of the butenolide. In this communication we address both of these issues and reveal new Lewis acid controlled reactions that achieve excellent stereocontrol in (1) the addition of aliphatic terminal acetylides to tetrahydrofuran-2-carbaldehydes and (2) complete regiocontrol in the alkylation of *epi*-chlorohydrin.

This synthesis of bullatacin began by double allylation of the easily prepared C2-symmetric bis-epoxide **2** to give the known diol **3** (Scheme 2).[5] The desymmetrization of **3** was accomplished by mono-acylation to give acetate **4** in quantitative yield.[6] The THF rings were constructed stepwise with complete stereocontrol using the cobalt-catalyzed aerobic oxidative cyclization reported by Mukaiyama.[7−9] With one alcohol of **6** protected as its TBS ether, Swern oxidation gave aldehyde **7**.

With the bis(THF) core **7** at hand, the stage was set for introduction of either side chain. Additions of aliphatic carbanions to bis(THF)-2-carbaldehydes (i.e., **7**, Scheme 2) are known to give poor stereoselectivity under standard chelation-controlled conditions. We are unaware of reagents for the selective addition of aliphatic organometallic reagents to bis(THF)-2-carbaldehydes such as **7** that give preferentially anti stereochemistry as required for the left-hand side.[10] Others have pioneered a solution to this problem (not shown) that involves an unselective Grignard addition to aldehyde **7**, oxidation of the secondary alcohol to the ketone, and stereoselective hydride reduction using L-selectride followed by Mitsunobu inversion, for a transformation that in principle should only require two steps.[11] We successfully employed this sequence during our initial investigations, but clearly a less laborious approach was desired.

In this regard, we report herein a practical and general alternative for this transformation that relies on our observation that aliphatic titanium acetylide **8** reacts with bis(THF) **7** to give **9** with high 10:1 anti selectivity and in good 85% isolated yield (96% based on either recovered starting material, Scheme 3). The stereochemistry was assigned by NMR analysis of esters of each diastereomer.[12]

The right-hand side of bullatacin requires syn stereochemistry from addition to aldehyde **10**, which was prepared in 78% yield from **9** by protecting group adjustments and Swern oxidation. Recently, syn alkylation of a related mono-THF aldehyde substrate by the Carreira zinc acetylide method was reported.[13] We were able to successfully reproduce those results with a model mono-THF substrate. However, application of the same conditions with bis(THF) aldehyde **10** failed, and others have commented on the difficulties

(4) For a lead reference, see: Abe, M.; Murai, M.; Ichimaru, N.; Kenmochi, A.; Yoshida, T.; Kubo, A.; Kimura, Y.; Moroda, A.; Makabe, H.; Nishioka, T.; Miyoshi, H. *Biochemistry* **2005**, *44*, 14898−14906.

(5) Robbins, M. A.; Devine, P. N.; Oh, T. *Org. Synth.* **1999**, *76* 101−109.

(6) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdensuren, B.; Nakamori, S. *Chem. Eur. J.* **2003**, *9*, 389−399. ref 2.

(7) Hanessian, S.; Roy, R. *Can. J. Chem.* **1985**, *63*, 163−72.

(8) Inoki, S.; Mukaiyama, T. *Chem. Lett*. **1990**, 67−70.

(9) Alternatively, preparing both THF rings concurrently in the same pot using identical oxidation conditions was significantly less efficient in our experience. Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron Lett*. **1999**, *40*, 977−980.

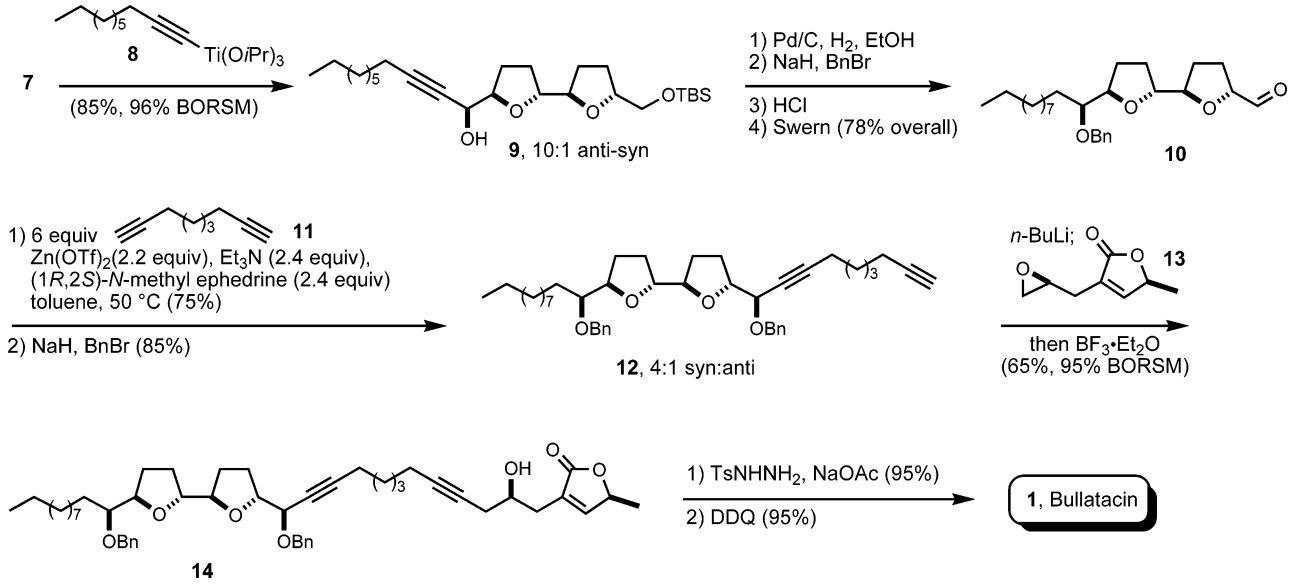
(10) (a) Emde, U.; Koert, U. *Eur. J. Org. Chem*. **2000**, 1889−1904. (b) Shunya, T.; Kenji, F.; Nobuo, S.; Tadashi, N. *Heterocycles* **2000**, *53*, 1361−1370.

(11) Harmange, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett*. **1992**, *33*, 5749−5752.

(12) (a) Ramirez, E. A.; Hoye, T. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1995; Vol 17, Structure and Chemistry (Part D), pp 251−282. (b) Gale, J. B.; Yu, J.-G.; Hu, X. E.; Khare, A.; Ho, D. K.; Cassady, J. M. *Tetrahedron Lett*. **1993**, *34*, 5847−5850. Amoroux, R.; Chastrette, F.; Chastrette, M. *J. Heterocycl. Chem*. **1981**, *18*, 565. Mulholland, R. L., Jr.; Chamberlain, A. R. *J. Org. Chem*. **1988**, *53*, 1082. A detailed discussion of all stereochemical assignments and comparisons to literature examples will be provided elsewhere.

(13) (a) Kojima, N.; Maezaki, N.; Tominaga, H.; Asai, M.; Yanai, M.; Tanaka, T. *Chem. Eur. J*. **2003**, *9*, 4980−4990. (b) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun*. **2004**, 406−407. (c) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc*. **1999**, *121*, 11245−11246.

Scheme 3. Modular Synthesis Based on the Bis(THF) **7**

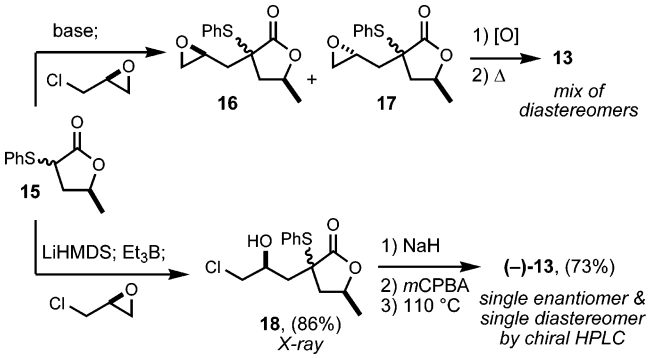


sometimes encountered with the alkyne addition.[14] After fruitless screening of stoichiometry and solvents, we found that with gentle heating the reaction ensued at 50 °C and the addition product **12** was obtained in 75% yield (syn:anti = 4:1).[15] Although the selectivity is lower for the bis(THF) substrate than for mono-THF systems, this approach is more efficient than Grignard addition, oxidation, and L-selectride reduction described above. Furthermore, results underscore the important reactivity differences between bis(THF)s and mono-THF 2-carbaldehydes.

Introducing the butenolide essentially intact (as **13**) by alkylation of **12** is a transparent strategy to enhance convergence of the synthetic stream (Scheme 3). However, this direct approach is seldom employed, and we were also reluctant to engage this route because an efficient synthesis of **13** is lacking. One difficulty arises from the poor regioselectivity in the alkylation of *epi*-chlorohydrin with **15**, which leads to the formation of epoxides **16** and **17** and ultimately to **13** as a mixture of diastereomers (Scheme 4, upper route).[16] This problem has prompted others to devise creative alternatives for accessing the same butenolide architecture, but none appear as concise and convergent as that detailed below.[17]

Advances in epoxide functionalization often arise from the judicious pairing of nucleophile and Lewis acid.[18] In this regard, we report herein a novel Et_3B-promoted regioselective alkylation of *epi*-chlorohydrin with the lithium enolate of White's lactone **15** to afford halohydrin **18**[19] in 86% isolated yield (Scheme 4, lower route). Closure of the halohydrin to the epoxide with NaH and elimination of the sulfoxide gave **13** in 99% ee and 63% yield overall from **15**. This modification is an important advance because it allows the most efficient synthesis to date of this useful butenolide epoxide.

Scheme 4. Regioselective Alkylation of *epi*-Chlorohydrin Mediated by Et_3B



Addition of the lithium acetylide of **12** (Scheme 3) with epoxide **13** cleanly afforded alcohol **14** in 65% isolated yield (95% yield based on either recovered starting material).[20] The natural product was ultimately revealed by reduction of

(14) For a literature summary and discussion, see Kirkham, J. E. D.; Courtney, T. D. L.; Lee V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219−7232.

(15) Recently, addition of a propargylic alkyne to a bis(THF) has been reported: Tominaga, H.; Maezaki, N.; Yanai, M.; Kojima, N.; Urabe, D.; Ueki, R.; Tanaka, T. *Eur. J. Org. Chem.* **2006**, 1422−1429.

(16) A related reverse alkylation strategy has been reported that circumvents *epi*-chlorohydrin, but translactonization then becomes problematic. (a) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. *Tetrahedron Lett.* **1994**, *35*, 8525−8528. (b) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. *Tetrahedron Lett.* **1994**, *35*, 8529−8532.

(17) (a) Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* **1998**, *39*, 9627−9628. (b) Trost, B. M.; Calkins, T. L. *Tetrahedron Lett.* **1995**, *36*, 6021−6024. (c) Schaus, S. E.; Brânalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876−4877 (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989−5995.

(18) Zhao, H.; Pagenkopf, B. L. *Chem. Commun.* **2003**, 2592−2593.

(19) The structure of **18** was confirmed by single-crystal X-ray analysis.

both alkynes with diimide followed by oxidative cleavage of the two benzyl ethers with DDQ (90% overall).[21]

In summary, a total synthesis of bullatacin from bis-epoxide **2** has been accomplished in 13.3% overall yield, which constitutes the most efficient synthesis of bullatacin to date by an order of magnitude. One streamlining feature that facilitated the synthesis is the stereoselective titanium acetylide addition to bis(THF) aldehyde **7**. The second is a short route to butenolide **13** made possible by a new Et_3B-mediated regioselective alkylation of *epi*-chlorohydrin. These tactics are being successfully applied to the synthesis of other annonaceous acetogenins and analogues, and these results will be reported in due course.

Acknowledgment. We thank the donors of the American Chemical Society Petroleum Research fund, Johnson and Johnson, NSERC, and the University of Western Ontario for financial assistance.

Supporting Information Available: General experimental procedures, characterization of all new compounds, and stereochemical analysis and X-ray structure data for **18** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061847O

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(21) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888. (b) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett*. **2003**, *5*, 3009−3011.