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An Efficient Synthesis of Epoxydiynes and a Key Fragment of Neocarzinostatin Chromophore

J. R. Baker,* O. Thominet, H. Britton, and S. Caddick*

Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1H OAJ, United Kingdom

s.caddick@ucl.ac.uk

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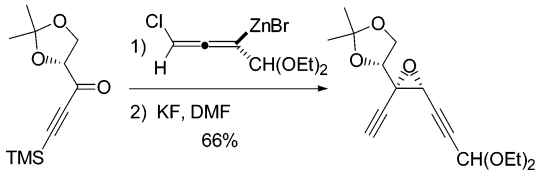
ABSTRACT



A key structural feature of the Neocarzinostatin chromophore is a reactive epoxydiyne. We present here a new method for the preparation of epoxydiynes by the addition of an allenyl zinc bromide to a propargylic ketone.

Neocarzinostatin (NCS), isolated from the bacterium *Streptomyces carzinostaticus* Var,[1] is a potent antibacterial and antitumor agent. NCS exists as a 1:1 complex of a protein and a highly reactive chromophore **1** (Figure 1). A polymer-

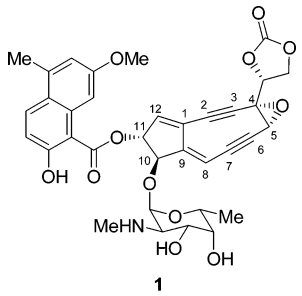


Figure 1. Neocarzinostatin chromophore.

conjugated version of the drug has been approved for treatment of a variety of cancers in Japan.[2] The cytotoxicity derives from the chromophore alone, while the protein component is required for its transportation and protection. The structure of the chromophore was elucidated in 1985 and found to contain an extremely strained epoxydiyne motif.[3]

NCS chromophore has been the subject of many synthetic studies in recent years,[4] culminating in two successful total syntheses to date by Myers[5] and Hirama.[6] Much of the work in this area has utilized epoxydiynes of the type **2** as key intermediates (Scheme 1). The synthesis of these compounds has been reported in 9−13 steps from the commercially available D-mannitol derivative **3**, applying sharpless epoxidations of enediynes as the key step in each case.[7]

Our own previous synthetic studies toward NCS chromophore have focused on a different strategy, involving a conjugate addition/intramolecular aldol sequence.[8] To extend

(1) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.

(2) Maeda, H.; Ueda, M.; Morinaga, T.; Matsumoto, T. *J. Med. Chem.* **1985**, *28*, 455−461.

(3) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331−334.

(4) (a) Myers, A. G.; Hammond, M.; Wu, Y. S.; Xiang, J. N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006−10007. (b) Bertus, P.; Pale, P. *Tetrahedron Lett.* **1997**, *38*, 8193. (c) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283−6306.

(5) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319−5320.

(6) Kobayashi, S.; Hori, M.; Wang, G. X.; Hirama, M. *J. Org. Chem.* **2006**, *71*, 636−644.

(7) (a) Hirama, M.; Wang, G. X.; Iguchi, S. *J. Org. Chem.* **2001**, *66*, 2146−2148. (b) Hirama, M.; Toyama, K.; Iguchi, S.; Sakazaki, H.; Oishi, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 997−1008.

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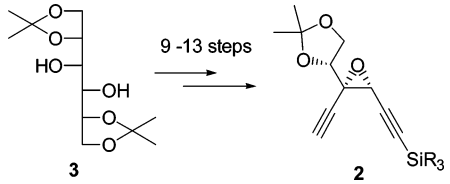
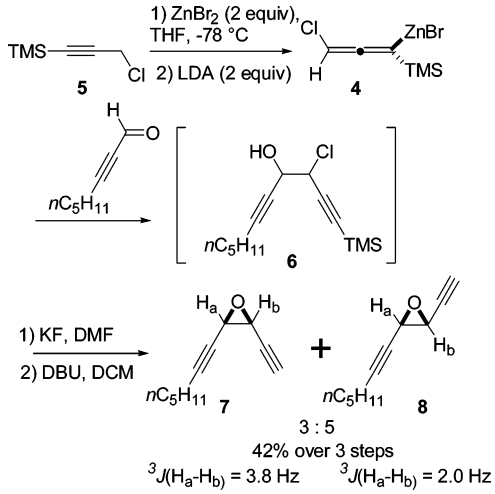
Scheme 1. Previous Routes to Key Epoxydiynes



this strategy we require the attachment of the C-8 carbon to the alkyne component prior to the union of the two fragments. This strategy requires that we find a general route to unsymmetrical epoxydiynes and despite considerable work we have been unable to extend any of the methods previously utilized for the synthesis of NCS chromophore and related structures. The purpose of this letter is to describe a new approach to unsymmetrical epoxydiynes that is not based on utilizing a Sharpless asymmetric epoxidation approach.

It has recently been reported that allenyl zinc bromide **4** can be added to a number of aldehydes and ketones to give halohydrins, which are subsequently cyclized to give propargylic epoxides.[9] Inspired by this work, we conceived of an approach to the desired epoxydiynes by addition of an allenyl zinc bromide to a propargyl ketone. Preliminary studies directed toward assessing the feasibility of this approach and in particular the stereochemical outcome were initiated. Treatment of propargyl chloride **5** with 2 equiv of zinc bromide followed by 2 equiv of LDA at low temperature led to the formation of an organozinc reagent, which we assumed to be **4** (Scheme 2). Addition of 2-octynal to this

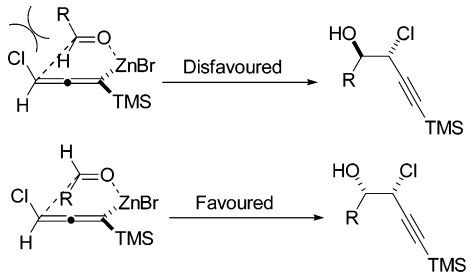
Scheme 2. Preparation of the Allenyl Zinc Bromide and the Synthesis of Simple Epoxydiynes



mixture led to the formation of two new products, proposed to be the diastereomers of chlorohydrin **6**. The crude mixture was treated with KF in DMF to afford the desilylated chlorohydrin, which was then cyclized with DBU.[10] The diastereomeric epoxides **7** and **8** were obtained as a mixture in a 3:5 ratio. Further purification allowed small amounts of each epoxide to be obtained separately, allowing full characterization. Thus the major product was confirmed as *trans* due to its smaller coupling constant.[11]

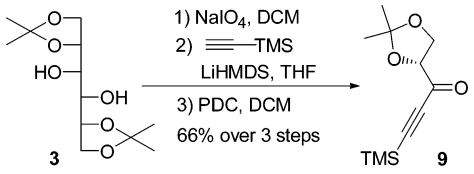
The stereochemical outcome is consistent with the major stereoisomer being generated from a transition state minimizing the steric interaction between the alkyne and the chlorine atom (Scheme 3).[9]

Scheme 3. Proposed Transition State Model for Selectivity



It was then considered that according to this transition state model, propargylic ketones including a bulky substituent in the α position would preferentially form the epoxide with the alkynes in a *cis* configuration. With NCS chromophore in mind the ketone **9** was synthesized from the D-mannitol derivative **3** via periodate cleavage of the diol, followed by the addition of TMS-acetylide and finally oxidation with pyridinium dichromate (Scheme 4).

Scheme 4. Synthesis of Chiral Ketone **9**



There was also literature precedent to presume that the chiral center at the α-position of **9** would guide the addition of the allenyl zinc species to the ketone to favor the resultant alcohol with the desired *R*-stereochemistry.[12] This can be rationalized by proceeding via the transition state shown in Scheme 5, following a nonchelation Felkin−Anh model or alternatively a *β*-chelation effect.

(8) Caddick, S.; Delisser, V. M.; Doyle, V. E.; Khan, S.; Avent, A. G.; Vile, S. *Tetrahedron* **1999**, *55*, 2737−2754.

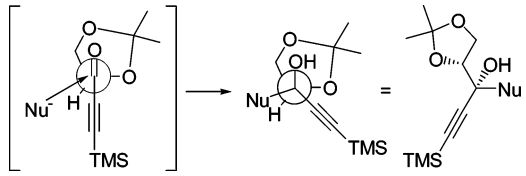
(9) (a) Chemla, F.; Bernard, N.; Ferreira, F.; Normant, J. F. *Eur. J. Org. Chem.* **2001**, 3295−3300. (b) Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539−570.

(10) Working up the desilylated intermediate and stirring it with a 10% NaOH solution led to an incomplete reaction after one week. This was also the case if the reaction was left stirring in DMF.

(11) $^3J_{cis} > {}^3J_{trans}$. Mortimer, F. S. *J. Mol. Spectrosc.* **1960**, *5*, 199−205.

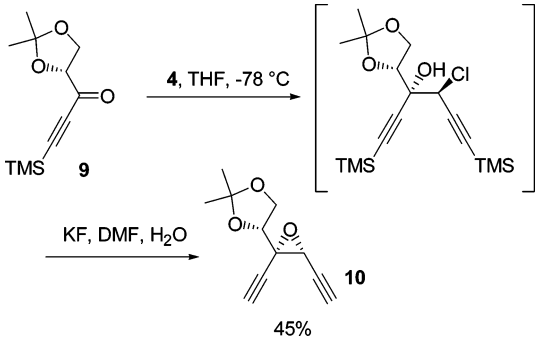
(12) (a) Kobayashi, S.; Das, P.; Wang, G. X.; Mita, T.; Lear, M. J.; Hirama, M. *Chem. Lett.* **2002**, 300−301. (b) Das, P.; Mita, T.; Lear, M. J.; Hirama, M. *Chem. Commun.* **2002**, 2624−2625. (c) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447−488.

Scheme 5. Proposed Stereoselective Nucleophilic Attack on **9**



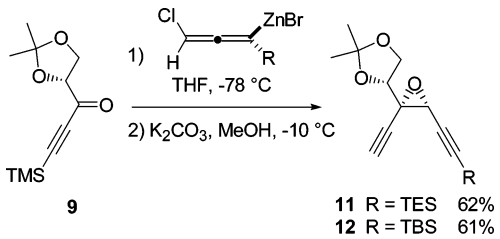
With four possible diastereomers obtainable in this reaction, it was promising to see one major chlorohydrin from crude NMR analysis. Subsequent treatment with KF led to the removal of both silyl groups and cyclization, to give a mixture of diastereomeric epoxydiynes of which only the desired product **10** was cleanly isolable in moderate yield (Scheme 6).[13] Confirmation of the stereochemistry of this product is discussed below.

Scheme 6. Addition to a Chiral Ketone



For this methodology to be generally useful, it needed to be applicable to unsymmetric disubstituted diyne epoxides. This methodology was therefore applied to the TES- and TBS-protected propargyl chlorides. In these cases the intermediate chlorohydrins were treated with K_2CO_3 at −10 °C to selectively remove the TMS groups. A mixture of diastereomeric epoxydiynes was formed in each of these reactions, from which the major components, **11** and **12**, respectively, were the only ones isolable (Scheme 7). It

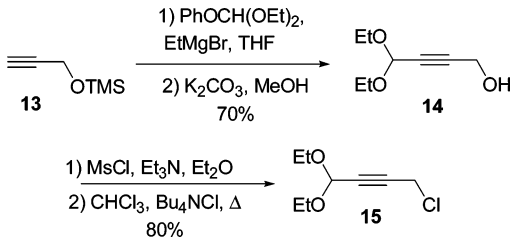
Scheme 7. Synthesis of Key Silylated Epoxydiynes



should be noted that the minor diastereomers in these reactions were present in complex mixtures, preventing their isolation and characterization, and thus reliable diastereomeric ratios could not be obtained. The stereochemistry of the isolated products in these cases could be confirmed as they are known compounds reported by Hirama[7b] and Myers,[4a] respectively. In the latter case the completion of the synthesis of Neocarzinostatin with this fragment unambigously confirmed the stereochemistry. Comparison of the α_D values of **11** and **12** with the literature also suggested no racemization of the chiral ketone **9** had taken place. The removal of the TES group from **11** with TBAF gave **10**, thus confirming the stereochemistry in the above case as well.

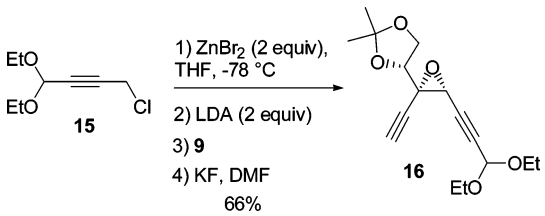
As mentioned previously, our general strategy toward NCS chromophore has been to include C-8 on the epoxydiyne fragment.[8] To do this using the allenyl zinc methodology required starting with an appropriately substituted propargylic chloride. This is a challenging test of the methodology, as it is complicated by the potential for cumulene formation. The required propargylic chloride **15** was readily made by treatment of commercially available alkyne **13** with diethylphenyl orthoformate and ethyl magnesium bromide followed by immediate desilylation to give acetal **14**.[14] Mesylation followed by displacement with chloride afforded the desired product **15** in good yield (Scheme 8).

Scheme 8. Synthesis of the Propargyl Chloride



As previously mentioned there was a possibility that on treatment with base that **15** would decompose via a cumulene intermediate. Gratifyingly, however, we found that treatment of **15** with $ZnBr_2$ and LDA, followed by propargyl ketone **9** led to chlorohydrin formation and subsequent treatment with KF afforded a mixture of diastereomeric epoxydiynes from which **16** was isolated in good yield (Scheme 9).

Scheme 9. A Key Fragment toward Neocarzinostatin



The addition of allenyl zinc bromides to alkynyl aldehydes and ketones offers a new method for the synthesis of

(13) Attempts to close the halohydrin with DBU led to a complex mixture of silylated and desilylated epoxide products being obtained.

(14) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791−2793.

epoxydiynes. This protocol provides a shortened synthesis of functionalized epoxydiynes which have found use in the synthesis of Neocarzinostatin chromophore. It has also proved possible to apply the method to form epoxydiynes containing a pendent acetal functionality. Studies are underway to apply this reaction in the total synthesis of NCS chromophore.

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Supporting Information Available: Full experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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