ORGANIC LETTERS

2011
Vol. 13, No. 16
4446–4449

Total Synthesis of (−)-Histrionicotoxin

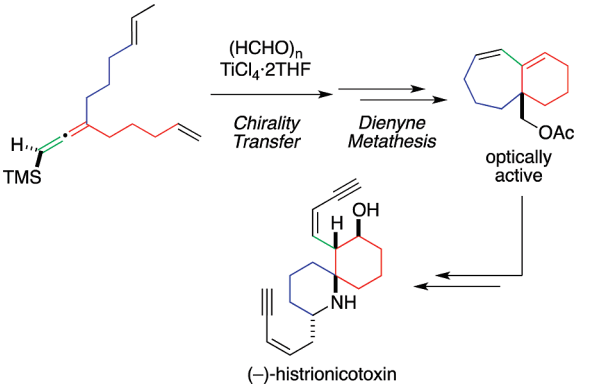
Yohei Adachi, Noriyuki Kamei,† Satoshi Yokoshima, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

Received July 6, 2011

ABSTRACT



A total synthesis of (−)-histrionicotoxin was achieved. Our synthesis features preparation of a pseudosymmetrical dienyne through chirality transfer from an allenylsilane, a dienyne metathesis to produce the bicyclo [5.4.0] system in optically active form, selective functionalization of a diene via a 5-exo-trig iodoetherification, and an asymmetric propargylation.

Histrionicotoxin (**1**) was isolated from the poison frog *Dendrobates histrionicus*, and its structure was characterized in 1971 by Daly and co-workers.[1] This small spirocyclic alkaloid is a noncompetitive inhibitor of the acetylcholine receptor, which results in neural toxicity.[2] The structure of histrionicotoxin (**1**), consisting of a 1-[5.5]undecane skeleton, two enyne side chains, and a secondary hydroxy group, poses multiple synthetic challenges. Histrionicotoxin has received considerable attention from the synthetic community, and a number of synthetic studies have been published to date.[3,4] Herein, we report an efficient total synthesis of (−)-histrionicotoxin (**1**), featuring the use of an optically active bicyclic intermediate **12**.

Our retrosynthesis is shown in Scheme 1. The two enyne side chains in **1** would be introduced by elongation of the aldehyde moieties in intermediate **2**, which would in turn be derived from bicyclo [5.4.0] system **3** via oxidative cleavage of the double bond. The nitrogen atom and the secondary hydroxy group in **3** would be introduced from precursor **4** via Curtius or Hofmann rearrangement of a carboxylic acid and hydroboration of a double bond, respectively. Construction of the bicyclo [5.4.0] system would be achieved by a dienyne metathesis[5] of

† Visiting researcher from Kaken Pharmaceutical Co., Ltd.

(1) Daly, J.; Karle, I.; Myers, C.; Tokuyama, T.; Waters, J.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.

(2) (a) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M.; Albuquerque, E. *Helv. Chim. Acta* **1982**, *65*, 252. (b) Gessner, W.; Takahashi, K.; Witkop, B.; Brossi, A.; Albuquerque, E. *Helv. Chim. Acta* **1985**, *68*, 49.

(3) For a review, see: (a) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298. For recent synthetic studies and syntheses of related compounds, see:(b) Macdonald, J. M.; Horsley, H. T.; Ryan, J. H.; Saubern, S.; Holmes, A. B. *Org. Lett.* **2008**, *10*, 4227. (c) Wilson, M. S.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 9601. (d) Brasholz, M.; Johnson, B. A.; Macdonald, J. M.; Polyzos, A.; Tsanaktsidis, J.; Saubern, S.; Holmes, A. B.; Ryan, J. H. *Tetrahedron* **2010**, *66*, 6445. (e) Brasholz, M.; Macdonald, J. M.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem.—Eur. J.* **2010**, *16*, 11471.

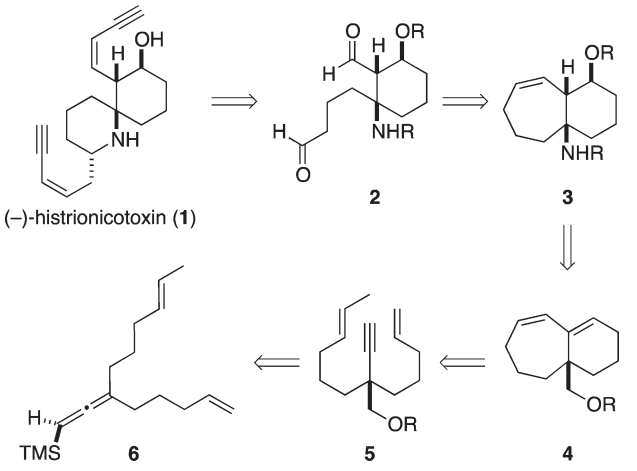
(4) For total syntheses, see: (a) Carey, S.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, *26*, 5887. (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (c) Williams, G.; Roughley, S.; Davies, J.; Holmes, A.; Adams, J. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (d) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656.

(5) (a) Kim, S.; Bowden, N.; Grubbs, R. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (b) Kim, S.; Zuercher, W.; Bowden, N.; Grubbs, R. *J. Org. Chem.* **1996**, *61*, 1073. (c) Boyer, F.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471. (d) Maifeld, S.; Lee, D. *Chem.—Eur. J.* **2005**, *11*, 6118. (e) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. (f) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55. (g) Lee, Y.-J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10652. (h) Niethe, A.; Fischer, D.; Blechert, S. *J. Org. Chem.* **2008**, *73*, 3088. (i) Park, H.; Hong, Y.-L.; Kim, Y. B.; Choi, T.-L. *Org. Lett.* **2010**, *12*, 3442. (j) Oguri, H.; Hiruma, T.; Yamagishi, Y.; Oikawa, H.; Ishiyama, A.; Otoguro, K.; Yamada, H.; Omura, S. *J. Am. Chem. Soc.* **2011**, *133*, 7096.

10.1021/ol2018032
Published on Web 07/27/2011

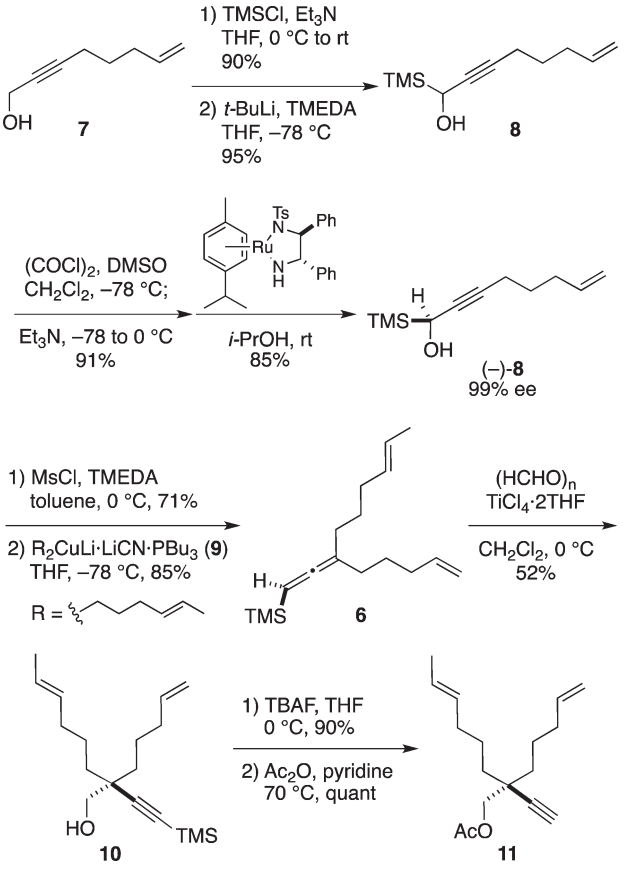
intermediate **5**. The terminal and internal double bonds in **5** could be differentiated by a metathesis catalyst to enable preparation of **4** in optically active form. Asymmetric synthesis of dienyne **5** containing a pseudosymmetric quaternary carbon posed a considerable challenge. We envisioned the preparation of this intermediate by means of chirality transfer from allenylsilane **6**.[6]

Scheme 1. Retrosynthesis



Our synthesis commenced with preparation of the optically active allenylsilane **6** (Scheme 2). After silylation of the known alcohol **7**,[7] treatment of the resulting trimethylsilyl ether with *t*-BuLi induced a retro-Brook rearrangement to afford alcohol **8**.[8] Swern oxidation of **8** followed by asymmetric reduction of the resulting ketone under Noyori transfer hydrogenation conditions[9] afforded the optically active alcohol (−)-**8** in 85% yield and in 99% ee.[10] Alcohol (−)-**8** was then converted to the corresponding mesylate, which, upon exposure to Lipshutz reagent **9**,[11] underwent

Scheme 2. Construction of the Quaternary Stereocenter



S_N2' reaction to furnish axially chiral allenylsilane **6** in optically active form.[12,13]

Having achieved the asymmetric synthesis of allenylsilane **6**, we next focused on hydroxymethylation of the allenylsilane through chirality transfer. While the synthesis of homopropargyl alcohols by addition of allenylsilanes to aldehydes was established by Danheiser and co-workers, only a few examples of 3,3-disubstituted allenylsilanes as substrates have been reported.[6d] In addition, these reactions were observed to be accompanied by the formation of dihydrofurans.[14] After screening a variety of conditions, we found that treatment of **6** with $TiCl_4 \cdot 2THF$ and paraformaldehyde in CH_2Cl_2 at 0 °C afforded homopropargyl alcohol **10** in

(6) (a) Carroll, L.; Mccullough, S.; Rees, T.; Claridge, T. D. W.; Gouverneur, V. *Org. Biomol. Chem.* **2008**, *6*, 1731. (b) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618. (c) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2009**, *11*, 4362. (d) Ogasawara, M.; Okada, A.; Subbarayan, V.; Soergel, S.; Takahashi, T. *Org. Lett.* **2010**, *12*, 5736.

(7) Salomon, R.; Coughlin, D.; Ghosh, S.; Zagorski, M. *J. Am. Chem. Soc.* **1982**, *104*, 998.

(8) (a) Speier, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 1003. (b) West, R.; Lowe, R.; Stewart, H. F.; Wright, A. *J. Am. Chem. Soc.* **1971**, *93*, 282. (c) Kruithof, K. J. H.; Klumpp, G. W. *Tetrahedron Lett.* **1982**, *23*, 3101. (d) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfune, Y. *Tetrahedron Lett.* **2000**, *41*, 6589.

(9) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.

(10) The absolute configuration of (−)-**8** was assigned based on the literature (ref 9) and was independently determined by application of the modified Mosher method. See Supporting Information. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

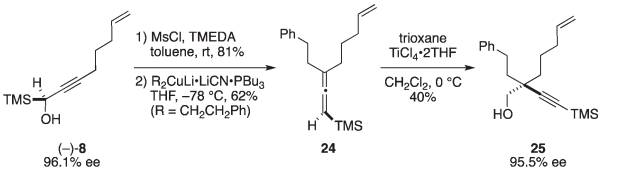
(11) Lipshutz, B.; Wilhelm, R.; Floyd, D. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(12) (a) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733. (b) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289. (c) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(13) Addition of BHT to the reaction mixture immediately after quenching was effective in preventing autooxidation of the allenylsilane during workup and purification. Yogo, T.; Koshino, J.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 769–774.

(14) (a) Danheiser, R.; Carini, D. *J. Org. Chem.* **1980**, *45*, 3925. (b) Danheiser, R.; Carini, D.; Kwasigroch, C. *J. Org. Chem.* **1986**, *51*, 3870.

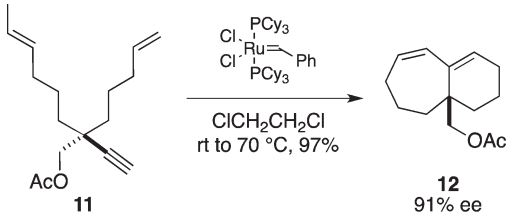
(15) The optical purity of **10** could not be determined because of its pseudosymmetrical structure. We confirmed that formation of allenylsilane **24** and its subsequent hydroxymethylation under similar conditions proceeded without significant loss of optical purity.



52% yield.[15] To our surprise, the product retained the TMS group. Therefore, the reaction seemed to proceed via a carbonyl-ene-type mechanism.[16] Desilylation of **10** with TBAF followed by acetylation afforded dienyne **11**.

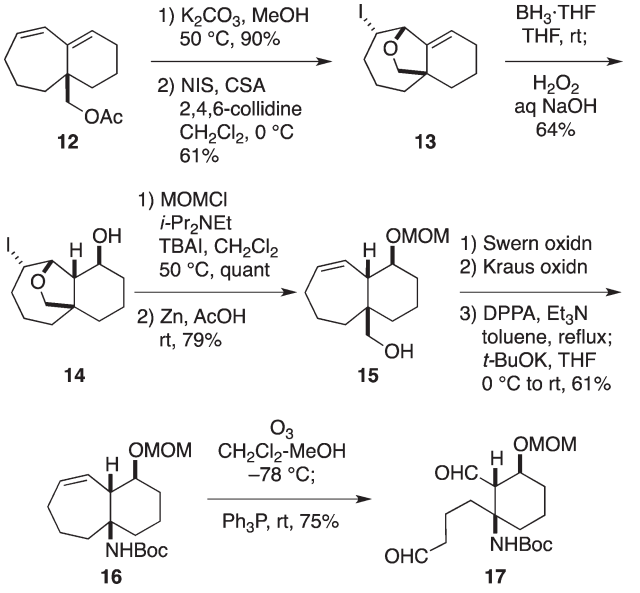
With the requisite dienyne **11** in hand, we turned to the key dienyne metathesis. It was expected that the dienyne metathesis would be initiated by coordination of a catalyst to the less substituted double bond[17] to afford the product in high enantiopurity. However, to the best of our knowledge, there has been no report of dienyne metathesis of optically active, pseudosymmetrical substrates such as **11**. We were gratified to find that heating **11** with a catalytic amount of the first-generation Grubbs catalyst[18] in 1,2-dichloroethane afforded **12** in 97% yield and in 91% ee (Scheme 3). It should be noted that the use of the second-generation Grubbs catalyst[19] or Hoveyda–Grubbs catalyst[20] provided the product in lower optical purities of 56% ee or 54% ee.[21]

Scheme 3. Construction of the Bicyclo [5.4.0] System



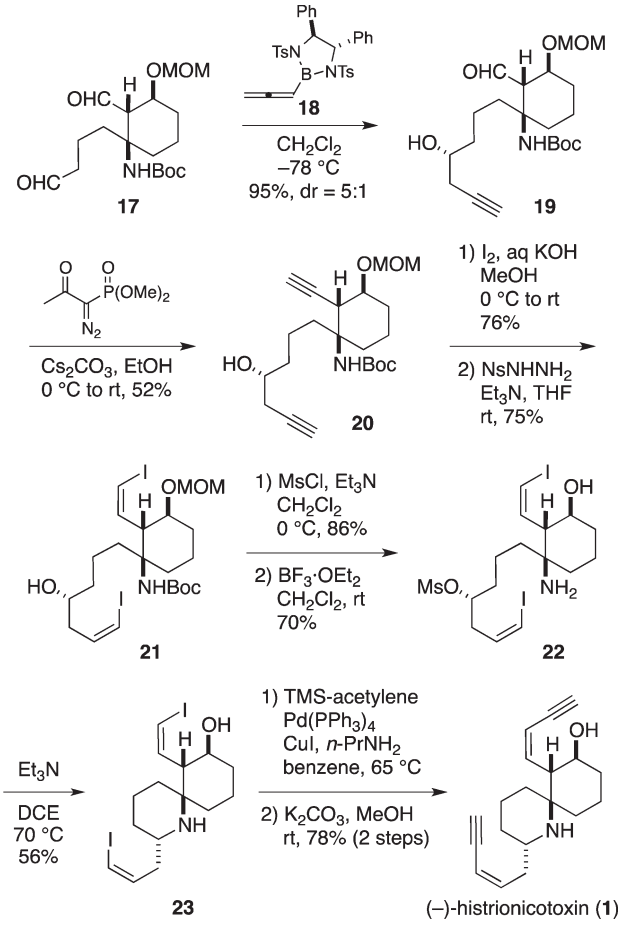
The next task was to selectively functionalize the two double bonds in **12** (Scheme 4). Methanolysis of acetate **12**, followed by treatment of the resulting alcohol with NIS in the presence of a weak acid, afforded iodoether **13** via a 5-exo-trig cyclization. Subsequent hydroboration of **13** proceeded regio- and stereoselectively to give **14** as a single isomer. After protection of the secondary hydroxy group as a MOM ether,[22] Zn-mediated reductive cleavage of the iodoether moiety produced **15**. Sequential oxidation[23] of the primary alcohol to the carboxylic acid and subsequent Curtius rearrangement furnished Boc amide **16**. Ozonolysis of **16** cleaved the remaining double bond to afford dialdehyde **17**.

Scheme 4. Selective Functionalization of the Double Bonds



The resultant dialdehyde was subjected to asymmetric propargylation. After evaluation of several reaction con-

Scheme 5. Completion of the Synthesis



(16) Weinreb, S.; Smith, D.; Jin, J. *Synthesis* **1998**, 509.
(17) Ulman, M.; Grubbs, R. *Organometallics* **1998**, *17*, 2484.
(18) Schwab, P.; France, M.; Ziller, J.; Grubbs, R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039.
(19) Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. *Org. Lett.* **1999**, *1*, 953.
(20) Garber, S.; Kingsbury, J.; Gray, B.; Hoveyda, A. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(21) The absolute configuration of **12** was determined after conversion into **14** by application of the modified Mosher method. See Supporting Information. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(22) The optical purity of the product was improved to 99% ee by precipitation of racemic crystals from hexane. For the detailed procedure, see Supporting Information.
(23) The sequential oxidation involved Swern oxidation and Kraus oxidation: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 to 0 °C; (b) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, *t*-BuOH-H_2O, 0 °C to rt, quant (2 steps). For the Kraus oxidation, see: (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (c) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (d) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

ditions,[24] we found that the method developed by Corey and co-workers[25] provided optimal results. Thus, upon treatment of **17** with chiral allenylborane **18**, propargylation occurred preferentially at the less hindered aldehyde to furnish a 5:1 diastereomeric mixture of homopropargyl alcohols **19** in 95% yield (Scheme 5). The product was then reacted with the Ohira–Bestmann reagent[26] in the presence of Cs_2CO_3 to afford diyne **20**.

To complete the total synthesis, the remaining transformations were elongation of the side chains and construction of the 1-azaspiro[5.5]undecane skeleton. Iodination of the terminal triple bonds of **20** using I_2 and KOH, followed by diimide reduction, gave diene **21**. After mesylation of the secondary hydroxy group, both the Boc and the MOM groups were removed by treatment with $BF_3 \cdot OEt_2$ to give **22**. Upon heating at 70 °C with triethylamine in 1,2-dichloroethane, amino-alcohol **22** underwent an intramolecular S_N2 reaction with inversion of the configuration to furnish **23**. Separation of the diastereomers by preparative TLC was performed at this stage. Finally, Sonogashira coupling with trimethylsilylacetylene and subsequent desilylation afforded (−)-histrionicotoxin (**1**). The spectral and physical data, including ^1H and ^{13}C NMR, IR, HRMS, and $[\alpha]_D$, were in accord with the reported data.

In conclusion, we have achieved an efficient total synthesis of (−)-histrionicotoxin (**1**). Key features of our synthesis include preparation of pseudosymmetrical dienyne **11** through chirality transfer from an allenylsilane, a dienyne metathesis to produce the bicyclo [5.4.0] system in optically active form, selective functionalization of the diene via a 5-exo-trig iodoetherification, and an asymmetric propargylation.

Acknowledgment. We thank Prof. Andrew B. Holmes at University of Melbourne for providing NMR spectra of histrionicotoxin. This work was financially supported in part by Grants-in-Aid (20002004) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, as well as by a grant from the Research Foundation for Pharmaceutical Sciences.

Supporting Information Available. Experimental details and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charges via the Internet at http://pubs.acs.org.

(24) (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (b) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173.

(25) Corey, E.; Yu, C.; Lee, D. *J. Am. Chem. Soc.* **1990**, *112*, 878.

(26) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Muller, S.; Liepold, B.; Roth, G.; Bestmann, H. *Synlett* **1996**, 521.