

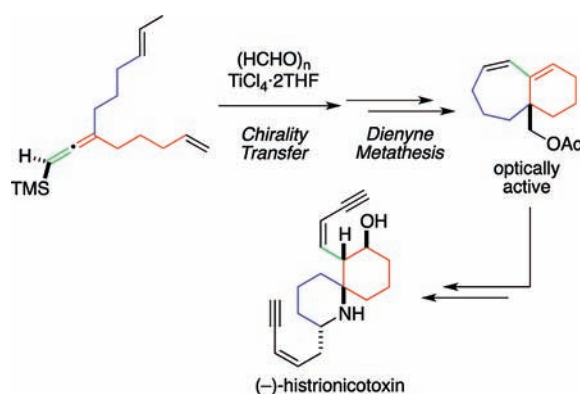
## Total Synthesis of (–)-Histrionicotoxin

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## 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.<sup>1</sup> This small spirocyclic alkaloid is a noncompetitive inhibitor of the acetylcholine receptor, which results in neural toxicity.<sup>2</sup> 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.<sup>3,4</sup> 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<sup>5</sup> of

<sup>†</sup> 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.

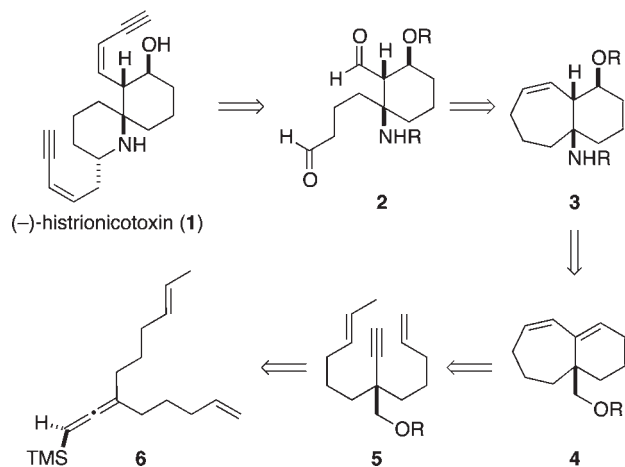
(3) For a review, see: (a) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298. For recent synthetic studies and syntheses of related compounds, see: (b) Macdonald, J. M.; Horsley, H. T.; Ryan, J. H.; Saubern, S.; Holmes, A. B. *Org. Lett.* **2008**, *10*, 4227. (c) Wilson, M. S.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 9601. (d) Brasholz, M.; Johnson, B. A.; Macdonald, J. M.; Polyzos, A.; Tsanaktisidis, 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.; Otaguro, K.; Yamada, H.; Omura, S. *J. Am. Chem. Soc.* **2011**, *133*, 7096.

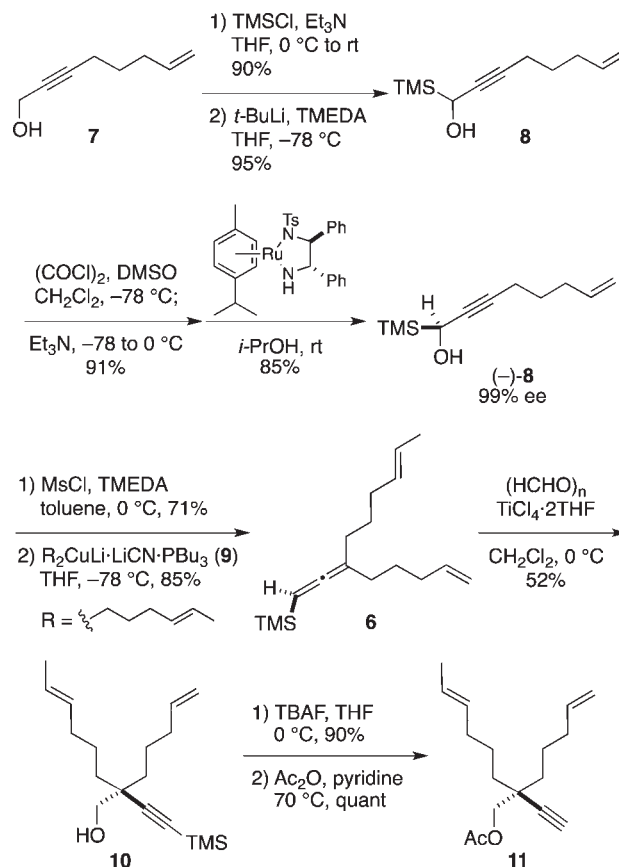
intermediate **5**. The terminal and internal double bonds in **5** could be differentiated by a metathesis catalyst to enable preparation of **4** in optically active form. Asymmetric synthesis of dienyne **5** containing a pseudosymmetric quaternary carbon posed a considerable challenge. We envisioned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

### Scheme 1. Retrosynthesis



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

### Scheme 2. Construction of the Quaternary Stereocenter



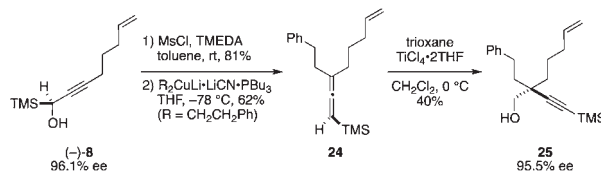
$S_N2'$  reaction to furnish axially chiral allenylsilane **6** in optically active form.<sup>12,13</sup>

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.<sup>6d</sup> In addition, these reactions were observed to be accompanied by the formation of dihydrofurans.<sup>14</sup> After screening a variety of conditions, we found that treatment of **6** with TiCl<sub>4</sub>·2THF and paraformaldehyde in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C afforded homopropargyl alcohol **10** in

(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.



(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) Kruthof, K. J. H.; Klumpp, G. W. *Tetrahedron Lett.* **1982**, *23*, 3101. (d) Sakaguchi, K.; Fujita, M.; Suzuki, H.; Higashino, M.; Ohfuné, 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.

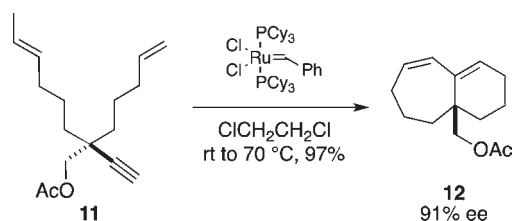
(11) Lipshutz, B.; Wilhelm, R.; Floyd, D. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(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.

52% yield.<sup>15</sup> To our surprise, the product retained the TMS group. Therefore, the reaction seemed to proceed via a carbonyl-ene-type mechanism.<sup>16</sup> 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<sup>17</sup> 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<sup>18</sup> 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<sup>19</sup> or Hoveyda–Grubbs catalyst<sup>20</sup> provided the product in lower optical purities of 56% ee or 54% ee.<sup>21</sup>

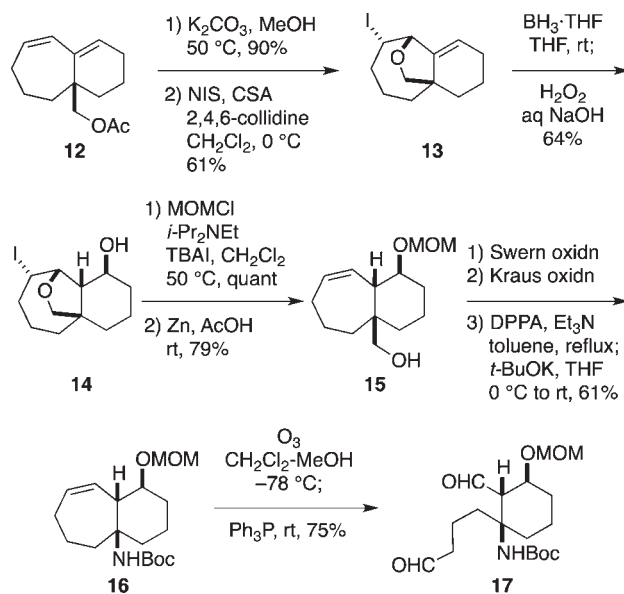
**Scheme 3.** Construction of the Bicyclo [5.4.0] System



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,<sup>22</sup> Zn-mediated reductive cleavage of the iodoether moiety produced **15**. Sequential oxidation<sup>23</sup> 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**.

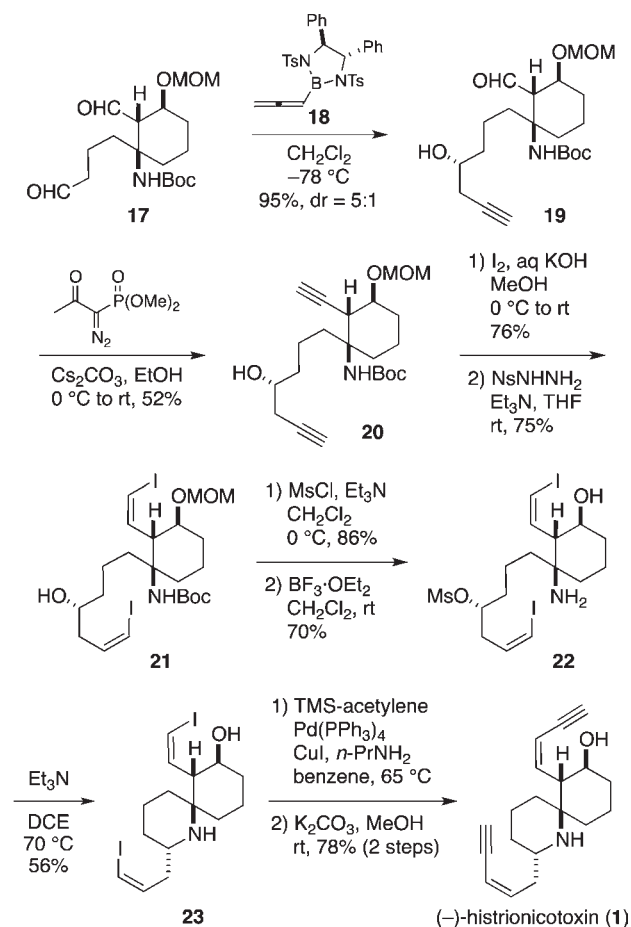
- (16) Weinreb, S.; Smith, D.; Jin, J. *Synthesis* **1998**, 509.  
 (17) Ulman, M.; Grubbs, R. *Organometallics* **1998**, *17*, 2484.  
 (18) Schwab, P.; France, M.; Ziller, J.; Grubbs, R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039.  
 (19) Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. *Org. Lett.* **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)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; Et<sub>3</sub>N, -78 to 0 °C; (b) NaClO<sub>2</sub>, 2-methyl-2-butene, NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, *t*-BuOH-H<sub>2</sub>O, 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.

**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



ditions,<sup>24</sup> we found that the method developed by Corey and co-workers<sup>25</sup> 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<sup>26</sup> in the presence of Cs<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub> 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<sub>3</sub>·OEt<sub>2</sub> to give **22**. Upon heating at 70 °C with triethylamine in 1,2-dichloroethane, amino-alcohol **22** underwent an intramolecular S<sub>N</sub>2 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 <sup>1</sup>H and <sup>13</sup>C NMR, IR, HRMS, and [α]<sub>D</sub>, 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 diyne **11** through chirality transfer from an allenylsilane, a diyne 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.

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**Supporting Information Available.** Experimental details and <sup>1</sup>H and <sup>13</sup>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.