## Selective Synthesis of Epolactaene Featuring Efficient Construction of Methyl (*Z*)-2-lodo-2-butenoate and (2R,3S,4S)-2-Trimethylsilyl-2,3-epoxy-4-methyl- $\gamma$ -butyrolactone

Ze Tan and Ei-ichi Negishi\*

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

negishi@purdue.edu

Received April 9, 2006

ABSTRACT



(+)-Epolactaene was synthesized in 14 steps in the longest linear sequence. The synthesis is highlighted by a highly efficient preparation of the lactone intermediate 4, which only requires three steps from the commercially available (*S*)-3-butyn-2-ol. It also features a fully stereocontrolled synthesis of the intermediate 9, which was constructed through the use of Zr-catalyzed methylalumination of alkynes and a series of Pd-catalyzed organozinc cross-coupling reactions, such as homopropargylation, direct ethynylation, and alkenylation of the methyl ester of (*Z*)- $\alpha$ -iodocrotonic acid (3).

Epolactaene (1) is a microbial metabolite isolated from the fungal strain *Penicillium* sp. BM 1689-P.<sup>1</sup> Because of its effectiveness in promoting neurite outgrowth and arresting the cell cycle at the G1 phase in a human neuroblastoma cell line, it has been considered for the treatment of neuro-degenerative diseases such as dementia.<sup>2</sup> It has also been found recently that epolactaene inhibits the activities of mammalian DNA polymerases and human DNA topo-isomerase II.<sup>3</sup>

Epolactaene (1) has previously been synthesized by three groups.<sup>4–6</sup> We became interested in the synthesis of 1 primarily because of the presence of a conjugated triene moiety featuring an  $\alpha$ -alkenylated (*E*)-crotonic ester, and we

(4) (a) Hayashi, Y.; Narasaka, K. Chem. Lett. **1998**, 313. (b) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. J. Org. Chem. **2002**, 67, 9443.

(5) (a) Marumoto, S.; Kogen, H.; Naruto, S. *J. Org. Chem.* **1998**, *63*, 2068. (b) Marumoto, S.; Kogen, H.; Naruto, S. *Tetrahedron* **1999**, *55*, 7129. (c) Marumoto, S.; Kogen, H.; Naruto, S. *Tetrahedron* **1999**, *55*, 7145.



hoped to prepare the side chain via a Pd-catalyzed  $\alpha$ -alkenylation<sup>7,8</sup> involving the use of **2** and **3** (Scheme 1). We

<sup>(1)</sup> Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. J. Antibiot. **1995**, *48*, 733.

<sup>(2) (</sup>a) Kakeya, H.; Onozawa, C.; Sato, M.; Arai, K.; Osada, H. J. Med. Chem. 1997, 40, 391. (b) Vatini, G.; Skaper, S. D. Pharmacol. Res. 1992, 26, 1. (c) Dicicco-Bloom, E.; Friedman, W. J.; Black, I. B. Neuron 1993, 11, 1101.

<sup>(3)</sup> Mizushima, Y.; Kobayashi, S.; Kuramochi, K.; Nagata, S.; Sugawara, F.; Sakaguchi, K. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 784.

<sup>(6) (</sup>a) Kuramochi, K.; Nagata, S.; Itaya, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, 40, 7367. (b) Kuramochi, K.; Nagata, S.; Itaya, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, 40, 7371. (c) Kuramochi, K.; Nagata, H.; Matsubara, Y.; Sunoki, T.; Uchiro, H.; Takao, K.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 9743.

<sup>(7)</sup> Negishi, E.; Alimardanov, A. In *The Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; J. Wiley & Sons: New York, 2002; Sect. III.2.14.2, pp 721–766.
(8) For α-alkenylation of carbonyl compounds by Negishi coupling,

<sup>(8)</sup> For  $\alpha$ -alkenylation of carbonyl compounds by Negishi coupling, see: (a) Negishi, E.; Owczarczyk, Z.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453. (b) Pour, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 4679. (c) Pour, M.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 525. (d) Negishi, E.; Pour, M.; Cederbaum, F. E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057. (e) Negishi, E.; Tan, Z.; Liou, S. Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.

also hoped to apply the Pd-catalyzed homoallyl—alkenyl coupling protocol developed by us<sup>9</sup> to the preparation of **2**. For the construction of the ring moiety and its union with the side chain, the strategy involving carbonyl addition of the oxiranyl anion derived from **4** reported by S. Kobayashi et al.<sup>6</sup> appealed to us as being convergent and fundamentally attractive. At the time our work was started, however, **4** had not been synthesized asymmetrically. Although their recent report<sup>6c</sup> described its synthesis, it required 12 steps from (*S*)-lactic acid ethyl ester.

We envisioned a short synthesis of (-)-4 via F. Sato's Ti-catalyzed trans-hydromagnesation of propargyl alcohol<sup>10</sup> and indeed achieved its synthesis in just three steps from commercially available (*S*)-3-butyn-2-ol in 32% overall yield, as outlined in Scheme 2. The crucial trans-hydromagnesation



with <sup>*i*</sup>BuMgCl in the presence of 3 mol % of Cp<sub>2</sub>TiCl<sub>2</sub> followed by carboxylation with CO<sub>2</sub> and lactonization proceeded in one pot in 71% yield. Epoxidation of the lactone thus obtained with NaOCl in pyridine at 0 °C afforded the desired product **4** as a single diastereoisomer in 51% yield.

A fully (>98%) stereocontrolled synthesis of **2** was achieved in seven steps by using the Zr-catalyzed carboalumination of alkynes<sup>11</sup> and the Pd-catalyzed cross-coupling with organozincs<sup>7–9</sup> as well as hydrozirconation<sup>12</sup> with HZrCp<sub>2</sub>Cl conveniently generated in situ by a recently developed <sup>*i*</sup>Bu<sub>2</sub>AlH–ZrCp<sub>2</sub>Cl<sub>2</sub> protocol<sup>13</sup> (Scheme 3). Although the preparation of **5**, specifically its modest yield of 55%, needs to be further improved, no delicate and potentially tedious stereo- or regioisomeric separation is required anywhere in the synthesis of **2**. To develop a more convergent route to **2**, 1-trimethylsilyl-6-iodo-3-hexen-1-yne (**6**) was prepared via hydrozirconation—iodinolysis of 4-iodo-1-butyne and a subsequent Pd-catalyzed alkynyl—alkenyl coupling<sup>14</sup> with TMSC=CZnBr. After lithiation with 'BuLi (2 equiv) and zincation with dry ZnBr<sub>2</sub>, its Pd-catalyzed cross-coupling with **5** led to a disappointingly low yield of TMS-protected **7** (41%) along with byproducts containing a cyclopropyl group. Evidently, metalation of **6** must be accompanied by metallotropy involving **8a** and **8b** (Scheme 3) similar to that reported previously by us in a related homoallyl—alkenyl cross-coupling reaction.<sup>9c</sup>

For conversion of **2** into the fully structured side chain **9**, we hoped to develop an efficient and selective synthesis of the methyl ester of (*Z*)- $\alpha$ -iodocrotonic acid (**3**) rather than its  $\alpha$ -bromo analogue, which was previously used by Kogen<sup>5b</sup> for the construction of the C1–C6 moiety via Stille coupling<sup>15</sup> in only 47% yield. To this end, methyl propiolate was carbocuprated with MeCu–TMEDA<sup>16</sup> and treated with I<sub>2</sub> to give >98% pure **3** in 62% yield (Scheme 4). Its cross-



coupling with the zinc derivative of **2** in the presence of 2.5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> and 10 mol % of tris(*o*-furyl)phosphine (TFP)<sup>17</sup> proceeded smoothly and selectively to give the desired cross-coupling product **10** in 76% yield. Noticing that Pd-catalyzed cross-coupling of  $\alpha$ -Bu<sub>3</sub>Sn-substituted methyl crotonate with a related dienyl iodide was reported to give a 91% yield of the C1–C10 fragment,<sup>6b</sup> we also ran the corresponding Stille reaction of **2**. In our hands, however,



the yield of 10 has been in the 70-80% range. Desilylation with TBAF followed by oxidation with MnO<sub>2</sub> provided 9 in  $\geq$ 98% isomeric purity in 72% yield over two steps (Scheme 4).

The final assembly of epolactaene from 4 and 9 was performed as summarized in Scheme 5 by closely following



the protocol developed by S. Kobayashi et al.6a,b The stereochemical details have been established by a combination of NOEs and coupling constant measurements performed on the lactone intermediate 11. Although efficient and

(11) (a) van Horn, D. E.; Negishi, E. J. Am. Chem. Soc. 1978, 100, 2252. (b) Negishi, E.; van Horn, D. E.; Yoshida, T. J. Am. Chem. Soc. 1985, 107, 6639. (c) Liu, F.; Negishi, E. J. Org. Chem. 1997, 62, 8591.

convergent, the yield over four steps has been limited to 18%, but it is comparable to that previously reported (15%). No efforts have been made in this study to further improve this part of the synthesis. Clearly, such efforts are highly desirable, and the efficient and selective synthesis of several key intermediates including 2-4, 9, and 10 herein reported should significantly facilitate such efforts. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of (+)-epolactaene obtained as a mixture of 1.8:1 epimers at C15  $[[\alpha]^{23}_{D} + 36.3^{\circ} (c \ 0.38 \text{ MeOH}) \text{ lit.}^{1}$  $[\alpha]^{22}_{D} + 32^{\circ}$  (c 0.1 MeOH)] match very well with those previously reported.4-6

Acknowledgment. We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research. Drs. F. Zeng and M. Qian performed related experiments not described in this paper. We thank Professor Susumu Kobayashi of Science University of Tokyo for providing us with valuable and helpful information.

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

## OL060856U

(12) (a) Hart, D. W.; Schwartz, J. J. Am. Chem. Soc. 1974, 96, 8115. (b) Schwartz, J.; Labinger, J. A. Angew. Chem., Int. Ed. Engl. 1976, 15, 333. (13) Huang, Z.; Negishi, E., submitted for publication.

(16) (a) Anderson, R. J.; Corbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Sidall, J. B. J. Am. Chem. Soc. 1975, 97, 1197. (b) Corey, E.; Katzenellenbogen, J. A. J. Am. Chem. Soc. 1969, 91, 1851.

(17) (a) Farina, V.; Baker, S. R.; Sapino, C., Jr. Tetrahedron Lett. 1988, 29, 6043. (b) Farina, V.; Krishnan, B. J. Am. Chem. Soc. 1991, 113, 9585.

<sup>(9) (</sup>a) Negishi, E.; Valente, L. F.; Kobayashi, M. J. Am. Chem. Soc. 1980, 102, 3298. (b) Kobayashi, M.; Negishi, E. J. Org. Chem. 1980, 45, 5223. (c) Negishi, E.; Liou, S. Y.; Xu, C.; Huo, S. Org. Lett. 2002, 4, 261

<sup>(10)</sup> Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. J. Chem. Soc., Chem. Commun. 1981, 718.

<sup>(14) (</sup>a) King, A. O.; Okukado, N.; Negishi, E. J. Chem. Soc., Chem. Commun. 1977, 683. (b) Kotora, M.; Xu, C.; Negishi, E. J. Org. Chem. 1997, 62, 8957. (c) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. Org. Lett. 2003, 5, 1597. (d) Negishi, E.; Anastasia, L. Chem. Rev. 2003, 103. 1979

<sup>(15) (</sup>a) Stille, J. K. Angew. Chem., Int. Ed. Engl. 1986, 25, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. Org. React. 1997, 50, 1.