

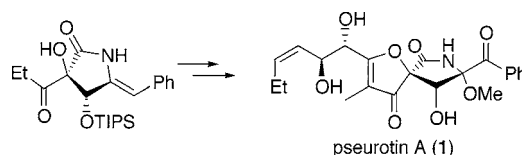
Asymmetric Total Synthesis of  
Pseurotin AYujiro Hayashi,<sup>\*,†</sup> Mitsuru Shoji,<sup>†</sup> Shinpei Yamaguchi,<sup>†</sup> Takasuke Mukaiyama,<sup>†</sup>  
Junichiro Yamaguchi,<sup>†</sup> Hideaki Kakeya,<sup>†</sup> and Hiroyuki Osada<sup>‡</sup>

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan, and Antibiotics Laboratory, Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

hayashi@ci.kagu.tus.ac.jp

Received April 11, 2003

## ABSTRACT



The asymmetric total syntheses of pseurotin A and 8-*O*-demethylpseurotin A have been accomplished. Key reactions are a NaH-promoted intramolecular cyclization of an alkynylamide to form a  $\gamma$ -lactam, an aldol reaction of a benzylidene-substituted ketone, and the late-stage introduction of the benzoyl group by a selective oxidation of a benzylidene moiety with dimethyldioxirane (DMD).

The pseurotins are a small family of secondary microbial metabolites isolated from a culture broth of *Pseudeurotium ovalis* (strain S2269/F) in 1976 by P. Bloch and C. Tamm et al.<sup>1</sup> Pseurotin A was reported to inhibit chitin synthase by Sterner et al. in 1993<sup>2</sup> and also found to induce cell differentiation of PC12 cells by Komagata et al. in 1995.<sup>3</sup> Structurally, it contains a novel, highly substituted, and oxygenated 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton with five chiral centers (Figure 1). The structure of pseurotin A, including its absolute stereochemistry, has been unambiguously determined by a single-crystal X-ray analysis of its 12,13-dibromo derivative.<sup>4</sup> Recently, azaspiroene, possessing the same core structure, has been isolated from the fungus *Neosartorya* sp. by Kakeya and Osada et al. and found to inhibit the endothelial migration induced by vascular

endothelial growth factor.<sup>5</sup> Because of the unprecedented, densely functionalized core structure of the pseurotins and azaspiroene, their total synthesis poses a significant challenge, and several synthetic endeavors aimed at the total synthesis of pseurotin A have been reported.<sup>6</sup> We have completed the first total synthesis of a member of this class of compounds, that of azaspiroene, in which a Sharpless asymmetric dihydroxylation, a MgBr<sub>2</sub>-mediated, highly diastereoselective Mukaiyama aldol reaction, and a NaH-mediated, intramolecular addition of an amide to an alkyne are employed as key steps.<sup>7</sup> Just recently, Tadano et al. have orally presented syntheses of pseurotin A and of 8-*O*-demethylpseurotin A<sup>2</sup> from D-glucose.<sup>8</sup> At the same time, as described in this paper, our group has also accomplished total syntheses of both pseurotin A and 8-*O*-demethylpseurotin A from the key intermediate in our synthesis of azaspiroene.

<sup>†</sup> Tokyo University of Science.<sup>‡</sup> RIKEN.

(1) (a) Bloch, P.; Tamm, C.; Bollinger, P.; Petcher, T. J.; Weber, H. P. *Helv. Chim. Acta*, **1976**, *59*, 133. (b) Bloch, P.; Tamm, C. *Helv. Chim. Acta*, **1981**, *64*, 304. (c) Breitenstein, W.; Chexal, K. K.; Mohr, P.; Tamm, C. *Helv. Chim. Acta*, **1981**, *64*, 379.

(2) Wenke, J.; Anke, H.; Sterner, O. *Biosci. Biotech. Biochem.* **1993**, *57*, 961.

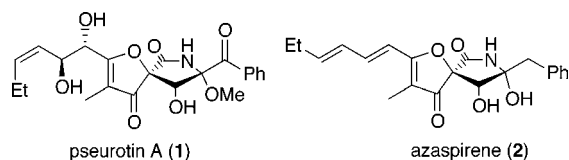
(3) Komagata, D.; Fujita, S.; Yamashita, N.; Saito, S.; Morino, T. *J. Antibiot.* **1996**, *49*, 958.

(4) Weber, H. P.; Petcher, T. J.; Bloch, P.; Tamm, C. *Helv. Chim. Acta*, **1976**, *59*, 137.

(5) Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4*, 2845.

(6) (a) Dolder, M.; Shao, X.; Tamm, C. *Helv. Chim. Acta*, **1990**, *73*, 63. (b) Shao, X.; Dolder, M.; Tamm, C. *Helv. Chim. Acta*, **1990**, *73*, 483. (c) Su, Z.; Tamm, C. *Helv. Chim. Acta*, **1995**, *78*, 1278. (d) Su, Z.; Tamm, C. *Tetrahedron* **1995**, *51*, 11177. (e) Aoki, S.; Ohi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Heterocycles* **2002**, *58*, 57.

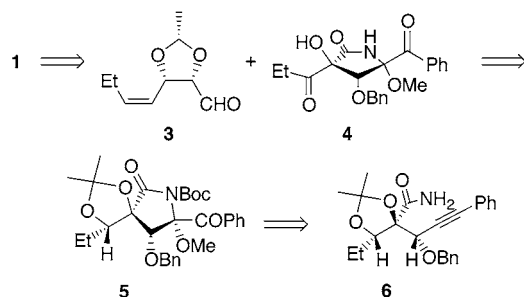
(7) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078.



**Figure 1.** Structures of pseurotin A and azaspirene.

Our retrosynthetic analysis is as follows: Pseurotin A might be prepared by consecutive aldol and dehydration reactions between side-chain aldehyde **3**<sup>6a</sup> and an ethyl ketone containing the fully functionalized  $\gamma$ -lactam moiety **4**, which in turn could be synthesized from  $\gamma$ -lactam **5**. It should be possible to prepare  $\gamma$ -lactam **5** from our synthetic intermediate for azaspirene **6**<sup>7</sup> by functional group transformation (Scheme 1).

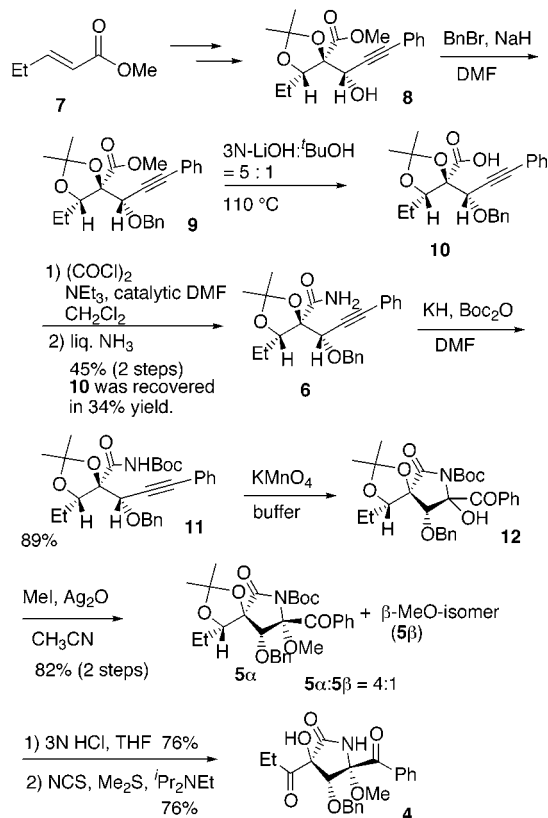
**Scheme 1.** First Retrosynthesis of Pseurotin A



The synthesis of ethyl ketone **4** starts from methyl pentenoate and follows our procedure for azaspirene up to alcohol **8** (Scheme 2).<sup>7</sup> The hydroxy group of **8** was protected using benzyl bromide and NaH. Although attempts at the direct conversion of ester **9** into amide **6** by literature procedures proved to be fruitless due to steric hindrance around the ester moiety, a two-step transformation worked well; the hydrolysis of ester **9** to carboxylic acid **10**, conversion to the acid chloride, and treatment with ammonia afforded amide **6** in 45% yield, with recovery of carboxylic acid **10** in 34% yield. The relative stereochemistry of **6** has been unambiguously determined by a single-crystal X-ray analysis.<sup>9</sup> Protection of amide **6** with the Boc group by KH and Boc<sub>2</sub>O and oxidation of the alkyne with KMnO<sub>4</sub> in acetone–buffer solution<sup>10</sup> gave a single isomer **12**, the stereochemistry of which has not been determined. Treatment of **12** with MeI and Ag<sub>2</sub>O<sup>11</sup> afforded the methyl ethers **5 $\alpha$**  and **5 $\beta$**  in 82% yield with the desired isomer predominating (**5 $\alpha$** :**5 $\beta$**  = 4:1). Removal of the acetonide and Corey–Kim

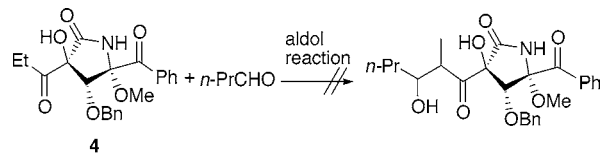
oxidation<sup>12</sup> of the secondary alcohol afforded ethyl ketone **4** containing the fully functionalized  $\gamma$ -lactam moiety.

**Scheme 2.** Synthesis of  $\gamma$ -Lactam **4**



With a practical route to ethyl ketone **4** in hand, its aldol condensation with *n*-butanal, a model aldehyde, was intensively investigated. Despite extensive experimentation on this key aldol reaction, the desired aldol product could only be obtained in low yield, with mostly decomposition of the  $\gamma$ -lactam moiety occurring at the stage of enolate generation (Scheme 3). The Mukaiyama aldol reaction cannot be

**Scheme 3.** Attempt of Aldol Reaction of **4**



examined because silyl enol ethers of **4** cannot be prepared even using Corey's in situ trapping method.<sup>13</sup> As we suppose that the benzoyl substituent causes the instability of ketone **4** under the basic conditions of enolate formation, we turned

(8) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Abstracts of Papers*, 44th Symposium on the Chemistry of Natural Products, Tokyo, Japan, 2002; p 73.

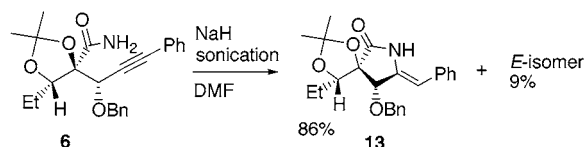
(9) Details of the crystallographic data, see ref 7.

(10) Srinivasan, N. S.; Lee, D. G. *J. Org. Chem.* **1979**, *44*, 1574.

(11) Greene, A. E.; Drian, C. L.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.

(12) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Corey, E. J.; Kim, C. U.; Misco, P. F. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 200.

(13) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

**Scheme 4.** Synthesis of Benzylidene  $\gamma$ -Lactam **13**

our attention to other ketones containing a synthetic equivalent of the benzoyl group.

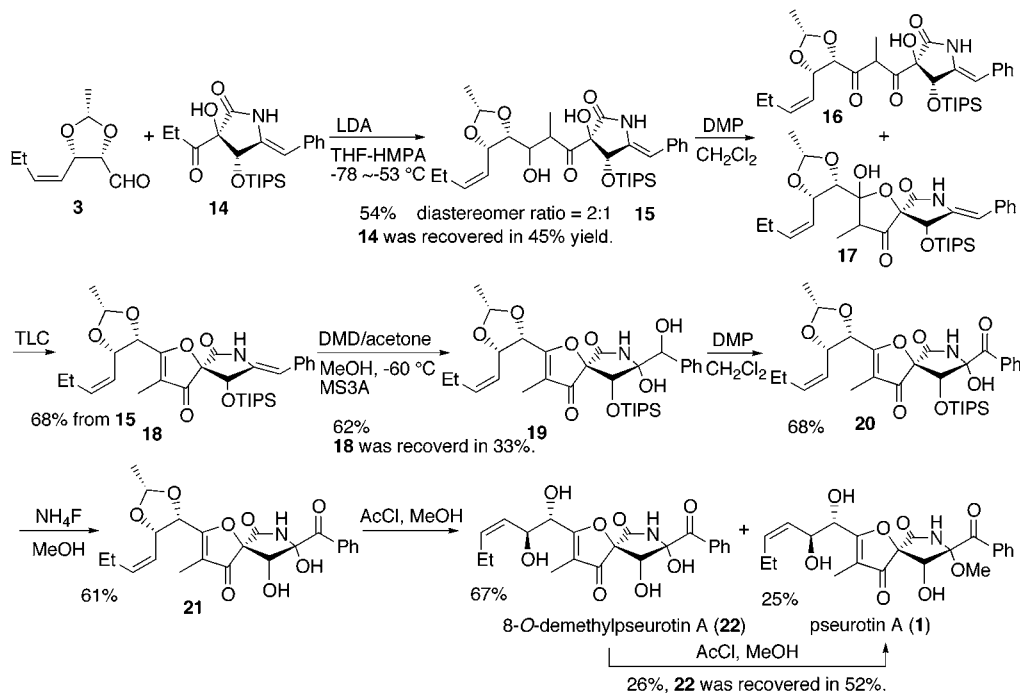
The unexpected experimental results described below promoted us to select a ketone with a benzylidene substituent as the aldol donor. In the previous transformation of **6** to **11**, Boc-protected amide **11** was obtained in good yield on treatment of amide **6** with KH in the presence of  $\text{Boc}_2\text{O}$ . Surprisingly, however, during the optimization of this step, it was found that benzylidene  $\gamma$ -lactam **13** was obtained in 51% yield without formation of the desired Boc-protected amide **11** when amide **6** was first treated with KH and then with  $\text{Boc}_2\text{O}$ . After screening the reaction conditions, we found that the yields of (*Z*)- and (*E*)- $\gamma$ -lactams **13** could be increased to 86 and 9%, respectively, when amide **6** was treated with NaH in DMF under ultrasound radiation (Scheme 4).

There are literature precedents for this intramolecular addition of an amide to nonactivated alkynes,<sup>14</sup> and this is a powerful method for construction of the  $\gamma$ -lactam portion. As the benzylidene moiety can be transformed into a benzoyl group by mild oxidation, this ketone containing a benzylidene moiety should be a suitable aldol donor. As benzyl (Bn) group could not be removed at the late stage of the synthesis,

ethyl ketone **14** having a triisopropylsilyl (TIPS) ether and a benzylidene group, which is a key intermediate in our total synthesis of azaspirene,<sup>7</sup> was employed as the aldol donor.

The lithium enolate of **14**<sup>7</sup> reacted with side-chain aldehyde **3** (*E*:*Z* = 4:1) prepared by the literature procedure,<sup>6a</sup> affording the aldol product **15** in 54% yield (diastereomeric ratio = 2:1) with recovery of ketone **14** in 45% yield (Scheme 5). Oxidation of aldols **15** with the Dess–Martin periodinane<sup>15</sup> (DMP) in  $\text{CH}_2\text{Cl}_2$  proceeded smoothly, providing 1,3-diketone **16**. <sup>1</sup>H NMR suggests that the oxidized product exists mostly in the 1,3-diketo form, rather than the keto–enol form. On attempting to purify **16** by thin-layer-chromatography (TLC), spiro compounds **17** and **18** were formed via cyclization and dehydration reactions due to the mild acidity of silica gel. Other acids such as *p*-TsOH·H<sub>2</sub>O and acetic acid were ineffective,<sup>16</sup> because side reactions such as hydration to benzylidene moiety and deprotection of acetonide took place. The second TLC treatment converted **17** to **18** completely (68% yield from **15**), with separation from the contaminating side-chain (*E*)-isomer.

The next task is selective oxidation of the benzylidene moiety without affecting the other olefinic parts. It was found that choice of oxidant and temperature are keys for the success of this reaction. Dimethyldioxirane<sup>14a,17</sup> (DMD) is the best oxidant, and when **18** was treated with DMD at low temperature ( $-60\text{ }^\circ\text{C}$ ) for 12 h in the presence of MS3A, diol **19** was obtained in moderate yield (62%) as a single isomer, the stereochemistry of which has not been determined, with recovery of the starting material **18** in 33% yield without formation of the methoxylactam. Diol **19** would be formed via opening of the intermediate epoxide with contaminating water.<sup>14a</sup> At higher temperatures or with

**Scheme 5.** Total Synthesis of Pseurotin A

prolonged treatment with DMD, the alkene in the side chain was also oxidized to its epoxide. Oxidation of alcohol **19** with DMP proceeded smoothly, affording benzoyl derivative **20** in moderate yield (68%).

Deprotection of the TIPS group, followed by treatment with AcCl in MeOH provided 8-*O*-demethylpseurotin A (**22**) and pseurotin A (**1**) in 67 and 25% yields, respectively. 8-*O*-Demethylpseurotin A (**22**) is also a natural product, isolated along with pseurotin A from submerged cultures of an osmophilic *Aspergillus fumigatus* strain and is an inhibitor of chitin synthase.<sup>2</sup> 8-*O*-Demethylpseurotin A (**22**) can be converted into pseurotin A (**1**) in 26% yield with recovery of 8-*O*-demethylpseurotin A (**22**) in 52% yield by acid treatment. Prolonged treatment of **22** with acid caused the rearrangement of allylic alcohol of the side chain. Synthetic

---

(14) (a) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855. (b) Cid, M. M.; Dominguez, D.; Castedo, L.; Vazquez-Lopez, E. M. *Tetrahedron* **1999**, *55*, 5599.

(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(16) Mild acidity of TLC can be successfully employed in our total synthesis of epolactaene for the hydrolysis of nitrile via intramolecular hydroxy group assistance; see: Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443.

(17) Adam, W.; Bialas, J.; Hadjarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

pseurotin A and 8-*O*-demethylpseurotin A exhibited properties identical to those of the natural products.

In summary, asymmetric total syntheses of pseurotin A (**1**) and of 8-*O*-demethylpseurotin A (**22**) have been achieved. There are several noteworthy features to the route used: the NaH-promoted intramolecular cyclization of an alkynylamide to form the  $\gamma$ -lactam **13**, the aldol reaction of ketone **14** containing a benzylidene group, and the late-stage introduction of a benzoyl group by the selective oxidation of this benzylidene moiety with DMD.

**Acknowledgment.** We thank Nippon Kayaku Co., Ltd., for a natural sample of pseurotin A. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**Supporting Information Available:** Detailed experimental procedures, full characterization, copies of <sup>1</sup>H and <sup>13</sup>C NMR and IR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL034630S