1918 J. Org. Chem. 1997, 62, 1918−1919

A Highly Efficient Synthesis of (−)-PI-091 Construction of the 4-Alkoxy-2-butene-4-lactam Skeleton from Fischer-Type Carbene Complexes, Alkynyllithiums, and Tosyl Isocyanate

Nobuharu Iwasawa* and Katsuya Maeyama

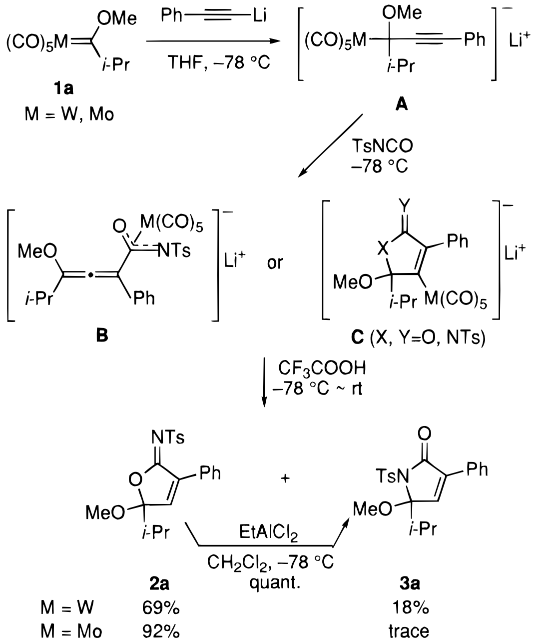
Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Received January 14, 1997

The 4-alkoxy-2-butene-4-lactam skeleton has attracted much attention because it forms the basic structure of several pharmacologically promising natural products such as PI-091,[1] epolactaene,[2] and so on.[3] However, the construction of this carbon framework with appropriate substituents is not necessarily easy, and multiple transformations are usually required.[4] In a previous paper, we reported that a new type of propargyl metallic species is generated by the addition of alkynyllithiums to Fischer-type carbene complexes and that these propargyl metallic species react with various carbon electrophiles such as aldehydes, sulfonylimines, and carbon dioxide to give furans, pyrroles, and 5-alkoxybutenolides, respectively.[5] We considered employing an isocyanate, a nitrogen analogue of carbon dioxide, as an electrophile with the expectation that the 4-alkoxy-2-butene-4-lactam skeleton bearing various substituents could be constructed in a single step. In this paper is described a successful realization of this approach and its application to a concise enantioselective synthesis of (−)-PI-091.

Examination of several isocyanates revealed that tosyl isocyanate[6] reacts with the propargyl metallic species generated from Fischer-type carbene complexes and alkynyllithiums. Thus, propargyl metallic species **A**, generated by the addition of (phenylethynyl)lithium to isopropylcarbene complex **1a** (M = W) at −78 °C, was reacted with tosyl isocyanate at this temperature overnight to give either an allenyl intermediate **B** or a [3 + 2] cycloaddition intermediate **C**.[6,7] The reaction mixture was then treated with trifluoroacetic acid to promote either cyclization (in the case of **B**) or protonation (in the case of **C**), giving a mixture of an *O*-cyclized product **2a** and an *N*-cyclized product **3a** in 69 and 18% yield, respectively (Scheme 1). When the corresponding molybdenum complex **1a** (M = Mo) was used for this reaction, the *O*-cyclized product **2a** was obtained in 92% yield, and only a trace amount of the *N*-cyclized product **3a** was produced.[8] Furthermore, it was found that the purified **2a** was quantitatively isomerized to **3a** by treatment with ethylaluminum dichloride in dichloromethane at −78 °C. To obtain the *N*-cyclized product **3a** selectively, the crude product of the addition reaction with tosyl isocyanate was directly treated with ethylaluminum dichloride in dichloromethane to give **3a** in 79% overall yield based on the carbene complex **1a** (M = Mo).

Scheme 1



We then examined the generality of this reaction. As summarized in Table 1, *N*-cyclized product **3** was obtained in good yields in every case.[9] Thus, this reaction is a highly efficient method for the construction of the 4-alkoxy-2-butene-4-lactam skeleton with various substituents from carbene complexes, alkynyllithiums, and tosyl isocyanate.

We next applied this reaction to the enantioselective synthesis of (−)-PI-091. PI-091 was isolated in 1990 by the research group at Taisho Pharmaceutical Co. from

---

* To whom correspondence should be addressed. Tel.: 81-3-3812-2111 ext 4643. Fax: 81-3-5800-6891. E-mail: niwasawa@chem.s.u-tokyo.ac.jp.

[1] Kawashima, A.; Yoshimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. Jpn. Kokai Tokkyo Koho JP 02 62859[90 62,-859](C1.C07D207/38), 02 Mar 1990, Appl. 88/215,393,30 Aug 1988; *Chem Abstr*. **1990**, *113*, 113856d.

[2] Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Okada, H. *J. Antibiot.* **1995**, *48*, 733.

[3] (a) Lam, Y. K. T.; Hensens, O, D.; Ransom, R.; Giacobbe, R. A.; Polishook, J.; Zink, D. *Tetrahedron* **1996**, *52*, 1481. (b) Singh, S. B.; Goetz, M. A.; Jones, E. T.; Bills, G. F.; Giacobbe, R. A.; Herranz, L.; Stevens-Miles, S.; Williams, D. L., Jr. *J. Org. Chem.* **1995**, *60*, 7040.

[4] Dittami, J. P.; Xu, F.; Qi, F.; Martin, M. W.; Bordner, J.; Decosta, D. L.; Kiplinger, J.; Reiche, P.; Ware, R. *Tetrahedron Lett.* **1995**, *36*, 4201. References are cited therein.

[5] Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* **1997**, *119*, 1486.

[6] For examples of the reactions of transition metal propargyl metallic species with tosyl isocyanate: (a) Giering, W. P.; Raghu, S.; Rosenblum, M.; Cutler, A.; Ehntholt, D.; Fish, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 8251. (b) Raghu, S.; Rosenblum, M. *J. Am. Chem. Soc.* **1973**, *95*, 3060. (c) Bell, P. B.; Wojcicki, A. *Inorg. Chem*. **1981**, *20*, 1585. (d) Shuchart, C. E.; Willis, R. R.; Wojcicki, A. *J. Organomet. Chem.* **1992**, *424*, 185. (e) Welker, M. E. *Chem. Rev.* **1992**, *92*, 97.

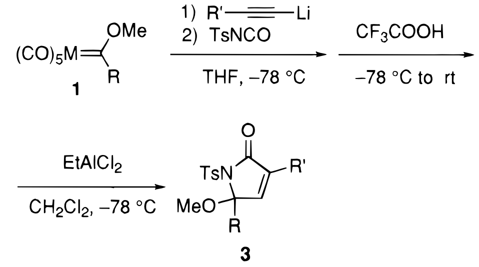
[7] We have not yet succeeded in isolating this intermediate.

[8] No isomerization of O-cyclized product **2a** to N-cyclized product **3a** was observed under these conditions (trifluoroacetic acid in THF at rt).

[9] The reaction was carried out as follows: To a THF solution (5 mL) of an alkyne (0.90−1.2 mmol) was added dropwise a 1.56 M hexane solution (0.40−0.53 mL, 0.62−0.83 mmol) of *n*-butyllithium at −78 °C. After the mixture was stirred for 30 min at this temperature, a THF solution (2 mL) of a tungsten or a molybdenum carbene complex (0.30 mmol) was slowly added. After the mixture was stirred for 1 h at −78 °C, a THF solution (4 mL) of tosyl isocyanate (2.0 mmol) was added and the mixture was stirred overnight at −78 °C. Trifluoroacetic acid (0.50 mL) was added at −78 °C, and the mixture was warmed to rt. After the mixture was stirred overnight at rt, triethylamine (1.0 mL) was added at 0 °C and then pH 7 phosphate buffer was added. The organic layer was extracted three times with ethyl acetate, and the combined extracts were dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in 10 mL of CH_2Cl_2 and a 1.0 M hexane solution of ethylaluminum dichloride (2.0 mL, 2 mmol) was added dropwise at −78 °C. After the mixture was stirred at this temperature for 3 h, 10% aqueous Rochelle salt solution was added carefully to the reaction mixture. The aqueous layer was extracted three times with ethyl acetate, and the combined extracts were dried over $MgSO_4$. After removal of the solvent, the residue was purified using preparative TLC (hexane:ethyl acetate = 6:4), yielding the corresponding *N*-cyclized product **3**.

S0022-3263(97)00068-6 CCC: $14.00

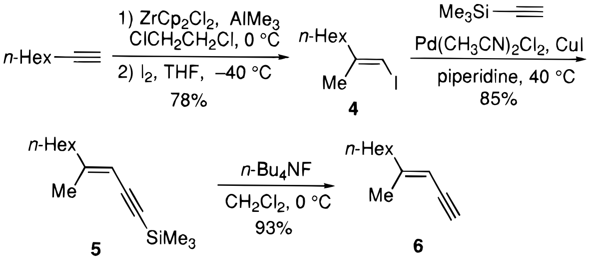
Table 1. Preparation of 4-Methoxy-2-butene-4-lactams



R	R′	M	yield of **3** (%)
i-Pr	Ph	Mo[a]	79 (**3a**)
i-Pr	*n*-Hex	Mo[a]	83
Ph	Ph	W	80
Ph	*n*-Hex	W	87

[a] The molybdenum complex gave slightly better yield than the corresponding tungsten complex.

Scheme 2



Paecilomyces sp. F-3430 and exhibits modest arachidonic acid-induced platelet aggregation−inhibitory activity.[1] PI-091 contains the 4-alkoxy-2-butene-4-lactam skeleton and was isolated as a 1:1 diastereomeric mixture at the *N*,*O*-acetal carbon. Tadano et al. have already reported the first total synthesis of PI-091 starting from D-glucose.[10]

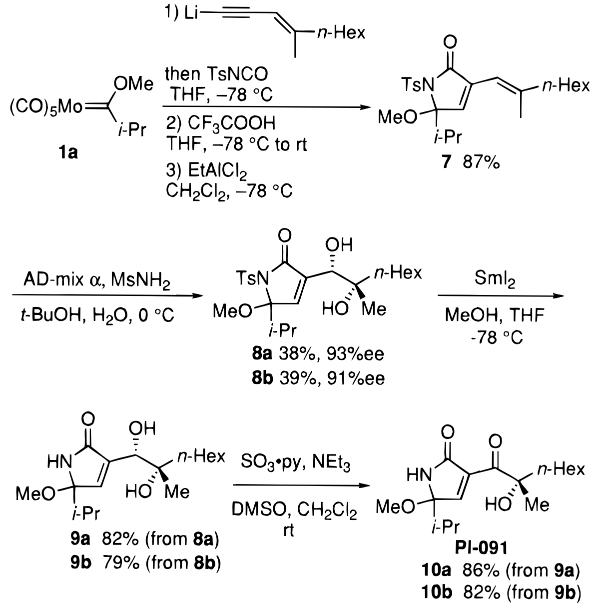
It was expected that the basic structure of PI-091 could be synthesized from the isopropyl carbene complex **1a**, (*E*)-4-methyl-3-decen-1-yne (**6**), and tosyl isocyanate by using our procedure.

The requisite enyne **6** was prepared in a straightforward manner as shown in Scheme 2. Methylalumination of 1-octyne was carried out employing trimethylaluminum and zirconocene dichloride, and the resulting alkenyl aluminum species was treated with iodine to give an alkenyliodide **4** in 78% yield.[11] It was then coupled with (trimethylsilyl)acetylene by using $Pd(CH_3CN)_2Cl_2$ and CuI in piperidine[12] to give **5**, which was desilylated by tetrabutylammonium fluoride to give the enyne **6** in 79% yield from **4**.

With the enyne **6** in hand, we examined formation of the 4-alkoxy-2-butene-4-lactam. According to the procedure described above, the lithiated enyne **6** was reacted with isopropylcarbene complex **1a** to generate a propargyl metallic species, and then tosyl isocyanate was added. After two successive acid treatments (trifluoroacetic acid and then ethylaluminum dichloride), the expected 4-alkoxy-2-butene-4-lactam **7** was obtained in 87% yield.

Conversion of this intermediate **7** to PI-091 was carried out in a straightforward manner as shown in Scheme 3.

Scheme 3



Regio- and enantioselective dihydroxylation of the side chain olefin was achieved by using AD-mix α[13] to give a diastereomeric mixture of diols **8a** and **8b**.[14] These two isomers were easily separated by TLC, and the optical purities of **8a** and **8b** were determined to be 93% ee and 91% ee by using chiral shift reagents $Eu(hfc)_3$ and $Pr(hfc)_3$, respectively. Although reductive removal of the tosyl group from **8** turned out to be quite troublesome due to facile over-reduction, finally it was found that samarium(II) diiodide in methanol gave about 80% yield of the deprotected product **9**. The final stage of the synthesis was the oxidation of the secondary hydroxyl group, which was carried out in good yield by using SO_3•pyridine in DMSO. The ^1H and ^{13}C NMR spectra and optical rotations of the products obtained, **10a** and **10b**, agreed well with those of the natural product.[15]

In conclusion, we have developed a facile method for the construction of the 4-alkoxy-2-butene-4-lactam skeleton by the reaction of the propargyl metallic species, generated from Fischer-type carbene complexes and alkynyllithiums, and tosyl isocyanate. Furthermore, a highly efficient total synthesis of PI-091 was achieved by using this method.

Acknowledgment. We are grateful to the Research Laboratories for Applied Biology, Taisho Pharmaceutical Co., Ltd. for donating ^1H and ^{13}C NMR spectra of PI-091. This work was financially supported in part by the Fujisawa Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Experimental procedures and spectroscopic data are included for compounds **2**−**10** (9 pages).

JO9700686

---

(10) (a) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 5551. (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845.

(11) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

(12) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(13) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768.

(14) Diastereomers arise from configuration at the *N*,*O*-acetal carbon. The relative stereochemistries of **8a** and **8b** were not determined.

(15) Although natural PI-091 is a mixture of diastereomers, both **10a** and **10b** show nearly the same optical rotation as the natural product.