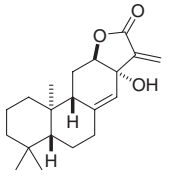
Total Synthesis of (–)-*ent*-Jolkinolide D

Kiyotake Suenaga, Yui Takayanagi, Masashi Yamaura, and Hideo Kigoshi*
Department of Chemistry, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba 305-8571

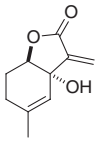
(Received May 7, 2004; CL-040513)

The first total synthesis of the enantiomer of jolkinolide D, a bioactive diterpene from *Euphorbia jolkini* Boiss, was achieved from abietic acid. The enantiomer did not exhibit the biological activities that the natural jolkinolide D possesses.

Jolkinolide D (**1**) is a diterpenoid isolated from *Euphorbia jolkini* Boiss in 1974,[1] and its stereostructure was recently determined by X-ray crystallographic analysis.[2] It exhibits cytotoxicity, inhibits tumor invasion into the basement membrane, and induces apoptosis in tumor cells.[2] Jolkinolide D (**1**) has a γ',δ'-unsaturated-β-hydroxy-α-methylene-γ-lactone unit as the pharmacophore structure, which suggests that jolkinolide D (**1**) might irreversibly alkylate biomolecules such as proteins and DNA in contrast to popular α-methylene lactones such as in germacranolides, eudesmanolides, guaianolides, and pseudoguaianolides[3] that would reversibly alkylate biomolecules. We have disclosed the alkylating activity of the pharmacophore **2** toward biomolecules, such as amino acids, peptides, nucleosides, and DNA.[4,5]



Jolkinolide D (**1**)



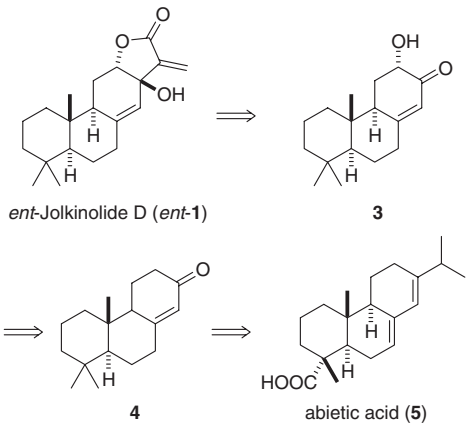
Jolkinolide D pharmacophore (**2**)

Because a comparison of the biological activities between the enantiomers would provide valuable information to understand the molecular mechanisms of the biological activities, we investigated the synthesis of optically active jolkinolides. So far, the total syntheses on jolkinolides have been reported for jolkinolides A, B, and E.[6–8] Herein we describe the first total synthesis of (–)-*ent*-jolkinolide D (***ent*-1**), the enantiomer of natural one.

In the previous paper,[4,5] we developed the construction of a γ',δ'-unsaturated-β-hydroxy-α-methylene-γ-lactone from a 2-cyclohexenone. Starting from the conjugated enone **4**,[9] prepared from abietic acid, this strategy affords the enantiomer of jolkinolide D (Scheme 1).

The conjugated enone **4** was prepared from abietic acid (**5**) by the reported procedure[9] with minor modification (Scheme 2). The ozonolysis of diene **6** was difficult to control to give the desired ketone **7**, especially in a small scale. So, we employed a sequence of OsO_4-$Pb(OAc)_4$ oxidations to afford **7** in good yield (85%), which was converted into the desired conjugated enone **4** (81%).

The conjugated enone **4** was converted into the corresponding silyl enol ether, which was transformed into α-hydroxy ketone **3** by oxidation and subsequent hydrolysis (55%). The stereochemistry of the hydroxy group in **3** was determined by a comparison of the spectral data with the reported[6–8] and the

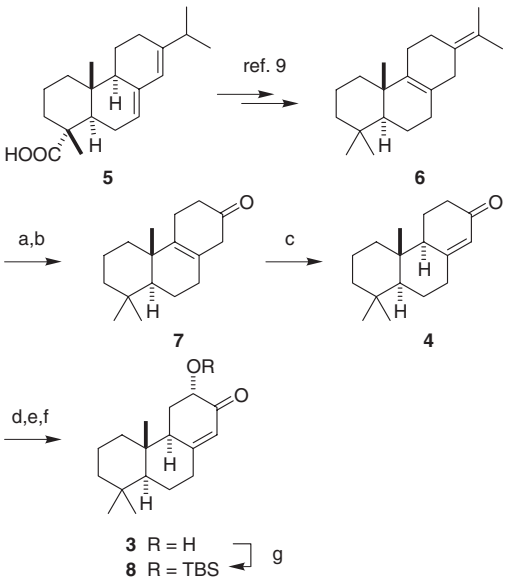


ent-Jolkinolide D (*ent*-**1**) **3** **4** abietic acid (**5**)

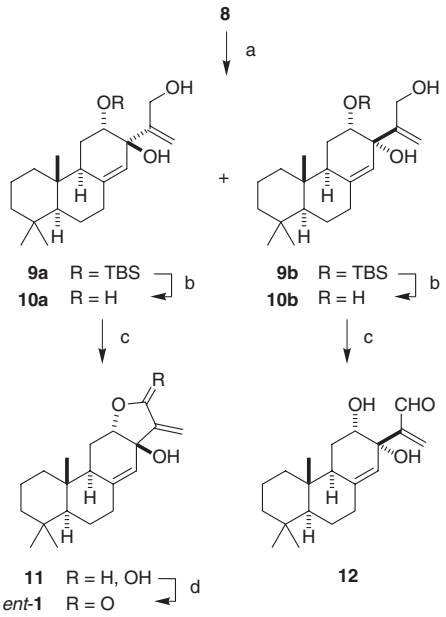
Scheme 1. Synthetic plan for *ent*-jolkinolide D (*ent*-**1**).

modified Mosher's method[10] to be *S*, arising from oxidation from less hindered side of the silyl enol ether. α-Hydroxy ketone **3** was silylated to give siloxy ketone **8**.

The coupling reaction between the hydroxy ketone **3** and an alkenyllithium reagent prepared from 2-iodoallyl alcohol gave diastereomeric alcohols **10a** and **10b** only in a poor yield (**10a**:**10b** = 3:2). On the other hand, the same coupling reaction



Scheme 2. Reagents and conditions: (a) OsO_4, pyridine, *t*-BuOH, rt, 1 h, 100%; (b) $Pb(OAc)_4$, benzene, 5 °C, 1 h, 85%; (c) HCl, MeOH, reflux, 1 h, 81%; (d) LDA, THF, −78 °C, 1 h; TESCl, rt, 1 h, 95%; (e) mCPBA, $NaHCO_3$, CH_2Cl_2, −50 °C to −30 °C, 2 h; (f) HF-Py, CH_2Cl_2, rt, 2 h, 57% (2 steps); (g) TBSCl, imidazole, rt, 1 h, 90%.



Scheme 3. Reagents and conditions: (a) 2-iodoallyl alcohol, *t*-BuLi, ether, 0 °C, 1 h, 36% (**9a**), 50% (**9b**); (b) TBAF, THF, 0 °C, 1 h, 100%; (c) MnO_2, $CHCl_3$, rt, 20 h, 79% (**12**); (d) MnO_2, $CHCl_3$, rt, 4 h, 99% (2 steps).

with the siloxy ketone **8** afforded **9a** (36%) and **9b** (50%) (Scheme 3). The stereochemistry of **9a** and **9b** could not be determined at this stage by the spectroscopic analysis. However, we can predict that the axial attack product might be predominant,[11] that is, the minor **9a** is the desired compound, which was confirmed by the synthetic reactions later. The stereochemistry of the secondary hydroxy group in **9a**, which might be epimerized under the basic conditions, was confirmed by the modified Mosher's method[10] again (Figure 1).

The final step of the synthesis has been established in the synthesis of **2**.[4,5] Whereas the major isomer **9b** was transformed into aldehyde **12** by desilylation and MnO_2 oxidation, the minor isomer **9a** was converted into hemiacetal **11**, oxidation of which afforded (–)-*ent*-jolkinolide D (***ent*-1**).[12] The synthetic jolkinolide D was found to be identical with natural one by a comparison of their spectroscopic data except for the sign of optical rotation: mp 198–199 °C (MeOH-ether), $[\alpha]_D^{23}$ −212 (*c* 0.090, $CHCl_3$).[13]

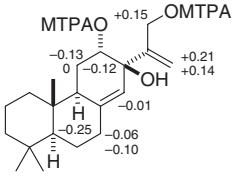


Figure 1. $\Delta\delta$ Values of the MTPA esters of **10a**.

The first total synthesis of the enantiomer of jolkinolide D, a bioactive diterpene of plant origin, was achieved from abietic acid. Preliminary investigation of the biological property revealed that ***ent*-1** did not induce apoptosis of U937 human leukemia at 10 μg/mL and did not inhibit tumor invasion into the basement membrane at 1 μg/mL while natural **1** exhibited both activities at the same concentration.[2] Further evaluation of biological activities are in progress.

We thank Prof. D. Uemura (Nagoya University) for providing us with natural jolkinolide D. We thank Screening Committee of New Anticancer Agents, supported by a Grant-in-Aid for Scientific Research on Priority Area "Cancer" from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for their biological tests. This work has been supported in part by the 21st Century COE program and Grant-in-Aid for Scientific Research (Ministry of Education, Culture, Sports, Science and Technology, Japan). Financial supports from Suntory Institute for Bioorganic Research, the Fujisawa Foundation, the Naito Foundation, University of Tsukuba Research Projects, and Wako Pure Chemical Industries, Ltd. are also acknowledged. The IR and NMR spectra were recorded at the Chemical Analysis Center, University of Tsukuba.

References and Notes

1 D. Uemura and Y. Hirata, *Chem. Lett.*, **1974**, 819.
2 H. Kigoshi, T. Ichino, K. Yamada, Y. Ijuin, S. F. Makita, and D. Uemura, *Chem. Lett.*, **2001**, 518.
3 N. H. Fischer, E. J. Oliver, and H. D. Fisher, *Fortschr. Chem. Org. Naturst.*, **38**, 47 (1979).
4 A. Sakakura, Y. Takayanagi, and H. Kigoshi, *Tetrahedron Lett.*, **43**, 6055 (2002).
5 A. Sakakura, Y. Takayanagi, H. Shimogawa, and H. Kigoshi, *Tetrahedron*, in press.
6 a) S. Katsumura and S. Isoe, *Chem. Lett.*, **1982**, 1689. b) S. Katsumura, A. Kimura, and S. Isoe, *J. Chem. Soc., Chem. Commun.*, **1983**, 330. c) S. Katsumura, A. Kimura, and S. Isoe, *Tetrahedron*, **45**, 1337 (1989).
7 T. Nakano and M. A. Maillo, *J. Chem. Res., Synop.*, **1985**, 268.
8 A. S. Demir, C. Tanyeli, H. Akgün, Z. Çaliskan, and E. Özgül, *Bull. Soc. Chim. Fr.*, **132**, 423 (1995).
9 A. Abad, M. Arno, L. Domingo, and R. Zaragoza, *Tetrahedron*, **41**, 4937 (1985).
10 I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **113**, 4092 (1991).
11 The conformational analysis of **3** and **8** by the ^{1}H NMR data indicated that the hydroxy group in **3** is oriented to equatorial while the siloxy group in **8** is oriented to axial; **3**: δ 4.31 (dd, J = 13.8, 6.8 Hz, 1 H), **8**: δ 4.09 (dd, J = 6.5, 3.8 Hz, 1 H).
12 For ***ent*-1**: UV (MeOH) λ_{max} 223 nm (ε 5520); IR (film) 3440, 2940, 2830, 1750, 1280, 1050 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 0.87 (s, 3 H), 0.90 (s, 3 H), 1.05–1.75 (m, 10 H), 1.91–2.41 (m, 4 H), 4.44 (t, J = 3.8 Hz, 1 H), 5.15 (d, J = 1.6 Hz, 1 H), 5.81 (s, 1 H), 6.20 (s, 1 H), one proton (–OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.1, 18.9, 21.4, 21.8, 22.2, 33.4, 33.7, 35.1, 37.6, 39.5, 41.8, 44.6, 54.0, 72.9, 81.0, 120.0, 120.7, 142.6, 144.8, 168.4; HRMS (ESI) m/z calcd for $C_{20}H_{28}NaO_3$ $(M + Na)^+$ 339.1936, found 339.1974.
13 For natural jolkinolide D:[1] mp 200–201 °C (MeOH-ether), $[\alpha]_D^{23}$ +218 (*c* 0.050, $CHCl_3$). Although the optical rotation was reported as $[\alpha]_D^{20}$ +360 (*c* 0.28, $CHCl_3$),[1] we found that it is as above for natural specimen provided by Prof. Uemura, Nagoya University.

Published on the web (Advance View) June 21, 2004; DOI 10.1246/cl.2004.918