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Enantioselective Total Synthesis of Eurylene, 14-Deacetyl Eurylene, and Their 11-Epimers: The Relation between Ionophoric Nature and Cytotoxicity

Hideaki Hioki,[†] Suzuyo Yoshio,[†] Masatoshi Motosue,[†] Yuka Oshita,[†] Yukari Nakamura,[†] Daisaku Mishima,[†] Yoshiyasu Fukuyama,[†] Mitsuaki Kodama,*[,†] Keisuke Ueda,[‡] and Takashi Katsu[‡]

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan, and Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700-8530, Japan

kodama@ph.bunri-u.ac.jp

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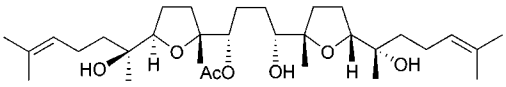
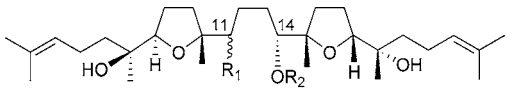
ABSTRACT



14-deacetyl eurylene

Enantioselective synthesis of eurylene, 14-deacetyl eurylene, and their 11-epimers was achieved. The characteristic structural feature of these compounds is two tetrahydrofuran (THF) rings substituted in different stereochemistry. The synthetic approach involves nonstereoselective THF ring formation to afford both segments from a common precursor. We also investigated their ionophoric nature and cytotoxicity. The complexation of these compounds with K^+ might be related to their cytotoxic activity.

Eurylene (**1**) and 14-deacetyl eurylene (**2**), shown in Figure 1, are triterpene polyethers isolated by Itokawa et al. from the wood of *Eurycoma longifolia* together with longilene peroxide and teurilene.[1] The structures of **1** and **2** were determined on the basis of spectroscopic analysis, X-ray crystallographic analysis of **1**, which was directly related to **2**, and modified Mosher's method. Because of the unique squalenoid polyether structures and biological activity (vide infra), synthetic studies were performed by various groups[2] and total syntheses of **1** by Ujihara et al.[2c] and of **2** by Morimoto et al.[2d] have been accomplished. In addition to the structure of **1** and **2**, Itokawa et al. discussed the relation between the cytotoxic activity and conformation of these triterpene polyethers on the basis of the findings that **1** has an extended conformation with essentially no cytotoxic activity (IC_{50} for KB cell: $>100\ \mu$g/mL), whereas **2**, as well as longilene peroxide and teurilene, has a folded conforma-



1:R_1=α-OAc, R_2=Ac **3**:R_1=β-OAc, R_2=Ac
2:R_1=α-OAc, R_2=H **4**:R_1=β-OAc, R_2=H

Figure 1. The structures of eurylene derivatives.

[†] Tokushima Bunri University.
[‡] Okayama University.

(1) (a) Itokawa, H.; Kishi, E.; Morita, H.; Takeya, K.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 1803−1804. (b) Itokawa, H.; Kishi, E.; Morita, H.; Takeya, K.; Iitaka, Y. *Chem. Lett.* **1991**, 2221−2222. (c) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765−771.

(2) For previous synthetic studies of eurylene, see: (a) Gurjar, M. K.; Saha, U. K. *Tetrahedron Lett.* **1993**, *34*, 1833−1836. (b) Molander, G. A.; Swallow, S. *J. Org. Chem.* **1994**, *59*, 7148−7151. (c) Ujihara, K.; Shirahama, H. *Tetrahedron Lett.* **1996**, *37*, 2039−2042. (d) Morimoto, Y.; Muragaki, K.; Iwai, T.; Morishita, Y.; Kinoshita, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4082−4084.

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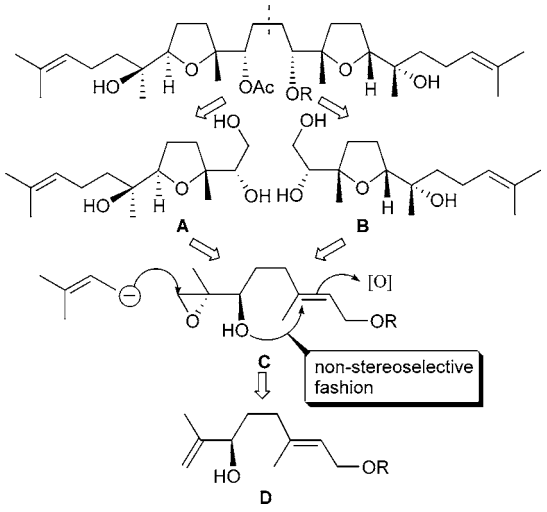
tion and possesses potent cytotoxicity (IC_{50} of **2** for KB cell: 0.52 μg/mL).[1c] Morimoto et al. suggested that the cytotoxic activities of **2,** longilenperoxide, and teurilene are caused by their ionophoric nature, that is, their ability to bind physiologically important divalent metal cations such as Mg^{2+} and Ca^{2+}.[3] There has been no experimental evidence, however, for this assumption.

In the course of our synthetic studies of natural products using bakers' yeast reduction as the chirality induction method,[4] we achieved enantioselective synthesis of **2**, which was transformed into **1** by Morimoto's group.[2d] In addition to **1** and **2**, their epimers at C-11 (**3** and **4)** were also simultaneously available from our synthesis. Therefore, we attempted to clarify the relation of the ionophoric complexing nature with cytotoxic activity. Our retrosynthetic analysis is illustrated in Scheme 1. Disconnection of the target molecules

Scheme 1. Retrosynthetic Analysis of Eurylene



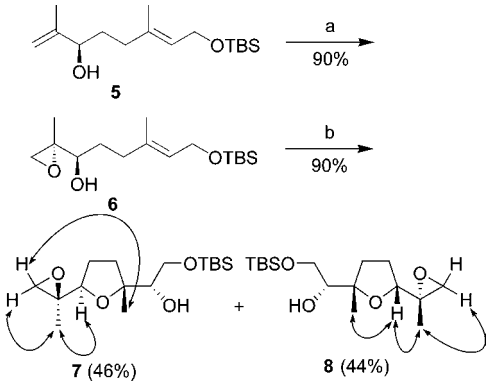
at the central part leads to two C-15 segments **A** and **B**. These diastereomeric segments are readily accessible from a common precursor, such as **C**, by the nonstereoselective THF ring formation followed by addition of a prenyl group.

7 and **8** were prepared from common precursor **6** (Scheme 2). The (*R*)-allylic alcohol **5**, obtained in more than 99% ee by using bakers' yeast reduction,[4a] was first converted into the epoxide **6** in 86% diastereomeric excess. Treatment of **6** with *m*CPBA afforded, as desired, two THF derivatives **7**

(3) Morimoto, Y.; Iwai, T.; Yoshimura, T.; Kinoshita, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2005−2010.

(4) (a) Kodama, M.; Minami, H.; Mima, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1990**, *31*, 4025−4026. (b) Kodama, M.; Yoshio, S.; Yamaguchi, S.; Fukuyama, Y.; Takayanagi, H.; Morinaka, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1993**, *34*, 8453−8456. (c) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117−118. (d) Kodama, M.; Yoshio, S.; Tabata, T.; Deguchi, Y.; Sekiya, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1997**, *38*, 4627−4630. (e) Hioki, H.; Ooi, H.; Hamano, M.; Mimura, Y.; Yoshio, S.; Kodama, M.; Ohta, S.; Yanai, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 1235−1246. (f) Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2552−2554. (g) Hioki, H.; Hamano, M.; Kubo, M.; Uno, T.; Kodama, M. *Chem. Lett.* **2001**, 898−899.

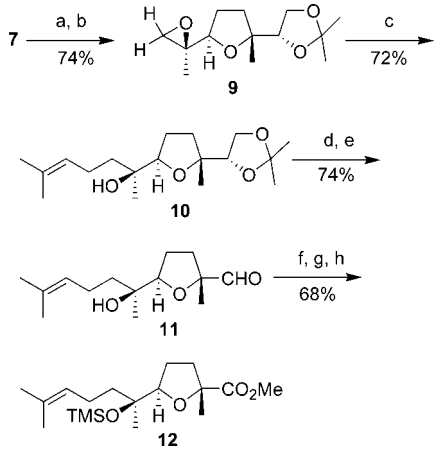
Scheme 2 Nonstereoselective THF Ring Formation[a]



[a] Reagents and conditions: (a) $VO(acac)_2$, *t*-BuOOH, benzene; (b) *m*CPBA, rt, CH_2Cl_2.

and **8** in almost equal amounts. The stereochemistry of these products was determined by NOE experiments (shown by the arrows in the structures). After the more polar product **7** was converted to **9** by sequential deprotection and protection of the resulting diol, the acetonide **9** was treated with prenylmagnesium chloride in the presence of cuprous iodide to yield the alcohol **10** in high yield. The acetonide protecting group in **10** was hydrolyzed and the resulting diol was cleaved to give the aldehyde **11**, which was further oxidized and esterified to give **12**, the left-half segment (Scheme 3).

Scheme 3. Synthesis of the Left-Half Segment[a]

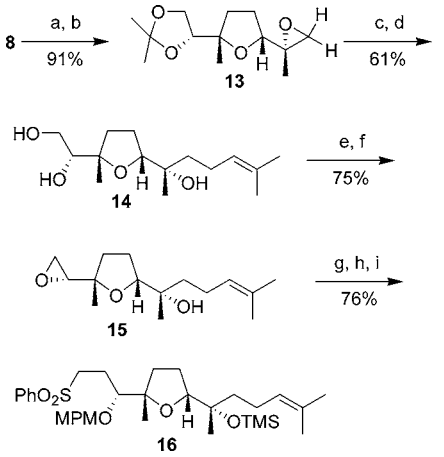


[a] Reagents and conditions: (a) *n*-Bu_4NF, THF; (b) DMP, PPTS, CH_2Cl_2; (c) $Me_2C{=}CHCH_2MgCl$, CuI, THF, −15 to 0 °C; (d) PPTS, EtOH; (e) $NaIO_4$, aq THF; (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, aq *t*-BuOH; (g) MeI, K_2CO_3, DMF; (h) TMSCl, Imid, DMF.

In a similar way, the less polar product **8** was transformed into the diol **14** through the acetonide **13** in 56% overall yield. The diol **14** was selectively converted into monomesylate, which was treated with base to yield the epoxide **15**. The lithio-anion of methylphenyl sulfone (2.5 mol equiv) was then reacted with **15** and two hydroxy groups were

protected by the *p*-methoxyphenylmethyl (MPM) group and trimethylsilyl (TMS) groups to complete the synthesis of the right-half segment **16** (Scheme 4).

Scheme 4. Synthesis of the Right-Half Segment[a]



[a] Reagents and conditions: (a) *n*-Bu_4NF, THF; (b) DMP, PPTS, CH_2Cl_2; (c) $Me_2C{=}CHCH_2MgCl$, CuI, THF, −15 to 0 °C; (d) PPTS, EtOH; (e) MsCl, Py; (f) K_2CO_3, MeOH; (g) $MeSO_2Ph$, *n*-BuLi, DMPU, THF, −78 to 0 °C; (h) MPMCl, NaH, DMF; (i) TMSCl, Imid, DMF.

A coupling reaction of the lithio-anion of **16** and **12** proceeded smoothly as shown in Scheme 5. After reductive desulfonylation and deprotection of the TMS group, ketone **17** was obtained in high yield. Reduction of **17** with $NaBH_4$ (95%) or DIBAH (91%) afforded an ca. 1:1 mixture of epimeric alcohols. Because these alcohols were difficult to separate, the mixture was acetylated and then separated to provide pure **18** and **19**. On deprotection of the MPM group, **18** and **19** afforded 14-deacetyl eurylene (**2**), mp 63.5−65 °C (lit.[1c] mp 63−65 °C), $[\alpha]^{19.3}_D$ +6.4 (lit. $[\alpha]^{19.3}_D$ +6;[1c] +6.02[2d]), and its epimer **4**, oil, $[\alpha]^{19.3}_D$ +26.0, respectively. Acetylation of **2** and **4** afforded eurylene (**1**), mp 149.5−150.0 °C (lit.[1a] mp 146−148 °C), $[\alpha]^{17.9}_D$ +8.1 (lit. $[\alpha]^{17.9}_D$ +4;[1a,2c] +4.86[2d]), and its epimer **3**, oil, $[\alpha]^{17.2}_D$ +31.2, respectively. The ^1H and ^{13}C NMR spectra of synthetic **1** and **2** were in excellent agreement with those of the natural products.

Following the synthesis of the four eurylene derivatives **1**−**4**, we studied the relationship between their ion transport abilities and cytotoxic activity. The ionophoric nature was evaluated in combination with ion-selective electrodes and liposomes.[5,6] In the present study, K^+,[7] Na^+,[8] and Ca^{2+} electrodes[9] were used to simultaneously monitor the movement of ions across the liposomal membrane composed of egg phosphatidylcholine. The results are shown in Table 1

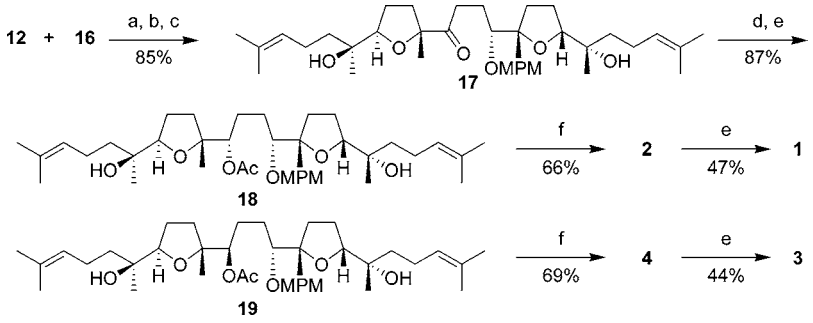
Table 1. Relation between Ion Transport Ability and Cytotoxic Activity of Eurylene Derivatives

	ion transport ability[a] (%)			IC_{50}[b]
compd	K^+	Na^+	Ca^{2+}	(μg/mL)
nonactin	40	24	8	
valinomycin	38	7	4	
eurylene (**1**)	1	0	0	>100
14-deacetyl eurylene (**2**)	14	2	1	13.6 ± 1.7
11-*epi*-eurylene (**3**)	7	1	0	8.9 ± 2.3
11-*epi*-14-deacetyl eurylene (**4**)	23	2	2	14.1 ± 2.1

[a] Expressed as percentage transported for 3 min. See Supporting Information for detailed experimental conditions. [b] IC_{50} (inhibitory concentration 50): values represent the drug concentration (±SD) required to reduce cell growth by 50% with respect to untreated controls.

together with those for nonactin and valinomycin, well-known ionophores.[10] Eurylene (**1**) had essentially no ability to transport any ions, while the other derivatives **2**−**4** acted as K^+-selective ionophores. In particular, **2** and **4** had strong K^+ transport ability, though the effects were weaker than that of valinomycin, a typical K^+-selective ionophore. The cytotoxic activities of compounds **1**−**4** on KB cells are shown in Table 1. Although 14-deacetyl eurylene (**2**) had over 20 times less activity than the reported value, the structure and activity relation between **1** and **2** are comparable to the reported data.[1c] 11-*epi*-Eurylene (**3**) exhibited higher cytotoxicity in contrast to **1**. The results show that

Scheme 5. Synthesis of Eurylene, 14-Deacetyl Eurylene, and Their 11-Epimers[a]



[a] Reagents and conditions: (a) LHMDS, DMPU, THF, −78 to −30 °C; (b) SmI_2, THF−MeOH (5:1), −78 °C; (c) 1 M HCl, MeOH; (d) $NaBH_4$, MeOH; (e) Ac_2O, Py, 50 °C; (f) DDQ, CH_2Cl_2−$NaHCO_3$ (10:1).

the stereochemistry at C-11 has an important role in the cytotoxicity.[11] On the other hand, the activity of 11-*epi*-14-deacetyl eurylene (**4**) was comparable to that of its 11-epimer (**2**). Some cytotoxic natural products involving the THF ring selectively form strong complexes with Ca^{2+}.[12] The bioactivity is postulated to be responsible for the metal ion complexation, which supports the idea that the cytotoxic activity of **2** might be due to its ionophoric nature.[3] Our results, however, demonstrated that cytotoxic compounds **2**−**4** are not Ca^{2+} ionophores but rather K^+ ionophores. The complexation with K^+ might be related to the cytotoxic activity.[13] The 11-*epi*-eurylene (**3**), however, had the most potent activity despite less ability to transport K^+ compared to 14-deacetyl derivatives **2** and **4**.

In conclusion, we completed the total asymmetric synthesis of four eurylene derivatives, **1**−**4**. Investigation of their ionophoric nature and cytotoxicity revealed K^+ ionophoric activity in the cytotoxic compounds **2**−**4**.

Acknowledgment. We thank Dr. Toshihiro Noguchi (Sumitomo Pharmaceuticals Co., Ltd., Japan) for the cytotoxicity testing and Prof. Koich Takeya (Tokyo University of Pharmacy and Life Science, Japan) for the NMR spectra of natural 14-deacetyl eurylene.

Supporting Information Available: Experimental conditions and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Barsukov, L. I.; Shkrob, A. M.; Bergel'son, L. D. *Biophysics* **1972**, *17*, 1032−1036.
(6) Katsu, T.; Nakashima, K. *Analyst* **1999**, *124*, 883−886.
(7) Katsu, T.; Kobayashi, H.; Fujita, Y. *Biochim. Biophys. Acta* **1986**, *860*, 608−619.
(8) Suzuki, K.; Sato, K.; Hisamoto, H.; Siswanta, D.; Hayashi, K.; Kasahara, N.; Watanabe, K.; Yamamoto, N.; Sasakura, H. *Anal. Chem.* **1996**, *68*, 208−215.
(9) Katsu, T.; Nakagawa, H.; Yasuda, K. *Antimicrob. Agents Chemother*. **2002**, *46*, 1073−1079.
(10) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501−530.
(11) To investigate the conformational difference between **1** and **3**, a Monte Carlo conformational search was performed employing the MM2 force field that is included with MacroModel software (v. 6.0). There was no significant conformational difference. The low-energy conformations of **1** and **3** are mainly folded conformations.
(12) (a) Sasaki, S.; Naito, H.; Maruta, K.; Kawahara, E.; Maeda, M. *Tetrahedron Lett*. **1994**, *35*, 3337−3340. (b) Peyrat, J.-F.; Figadere, B.; Cave, A.; Mahuteau, J. *Tetrahedron Lett*. **1995**, *36*, 7653−7656. (c) Peyrat, J.-F.; Mahuteau, J.; Figadere, B.; Cave, A. *J. Org. Chem*. **1997**, *62*, 4811−4815. (d) Sasaki, S.; Maruta, K.; Naito, H.; Maemura, R.; Kawahara, E.; Maeda, M. *Tetrahedron* **1998**, *54*, 2401−2410.
(13) Nonactin and valinomycin exhibited cytotoxicity against KB cells, see: Otake, N.; Sasaki, T. *Agric. Biol. Chem*. **1977**, *41*, 1039−1047.