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Stereoselective Total Synthesis of *ent*-EI-1941-2 and Epi-*ent*-EI-1941-2

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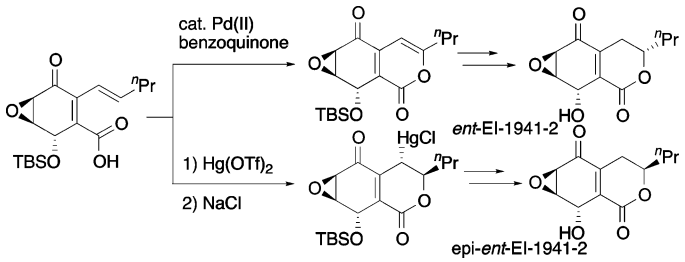
ABSTRACT



The first asymmetric total syntheses of *ent*-EI-1941-2 and epi-*ent*-EI-1941-2 have been accomplished, starting from a chiral epoxy iodoquinone 6, a key intermediate in our total syntheses of epoxyquinols A and B. A key step in the preparation of *ent*-EI-1941-2 is an intramolecular carboxypalladation via a 6-*endo* cyclization mode, followed by β-hydride elimination, while carboxymercuration is a key step in the synthesis of epi-*ent*-EI-1941-2.

Interleukin-1β (IL-1β) converting enzyme (ICE) is a cysteine protease that cleaves a biologically inactive 31 KDa precursor to biologically active IL-1β,[1] an important mediator in the pathogenesis of rheumatoid arthritis, septic shock, inflammation, and other physiological conditions.[2] Therefore, it is thought that ICE inhibitors would be useful as antiinflammatory drugs. Koizumi and co-workers have isolated EI-1941-1 (**1**), EI-1941-2 (**2**), and EI-1941-3 (**3**) from culture broths of *Farrowia* sp., the first two of which selectively inhibit human recombinant ICE activity with IC_{50} values of 0.086 and 0.006 μM, respectively.[3] Just recently, the relative and absolute stereochemistries of EI-1941-1 and -2 have been determined by X-ray crystallographic analysis of the *p*-bromobenzoyl ester of EI-1941-2.[4]

Structurally, EI-1941-1 and EI-1941-2 (Figure 1) have an epoxyquinone core, and due to our interest in the synthesis of such epoxyquinone derivatives, including ECH[5] and its dimers, epoxyquinols A and B,[6] we set out to accomplish the first asymmetric total synthesis of *ent*-EI-1941-2, the achievement of which will be disclosed in this paper.

A retrosynthetic analysis of EI-1941-2 is depicted in Scheme 1. At the time that we started this project, their

(1) (a) Thornberry, N. A.; Bull, H. G.; Calaycay, J. R.; Chapman, K. T.; Howard, A. D.; Kostura, M. J.; Miller, D. K.; Molineaux, S. M.; Weidner, J. R.; Aunins, J.; Elliston, K. O.; Ayala, J. M.; Casano, F. J.; Chin, J.; Ding, G. J.-F.; Egger, L. A.; Gaffney, E. P.; Limjuco, G.; Palyha, O. C.; Raju, S. M.; Roland, A, M.; Salley, J. P.; Yamin, T.-T.; Lee, J. A.; Shively, J. E.; Maccross, M.; Mumford, R. A.; Schmidt, J. A.; Tocci, M. J. *Nature* **1992**, *356*, 768. (b) Gerretti, D. P.; Kozlosky, C. J.; Mosley, B.; Nelson, N.; Ness, K. V.; Greenstreet, T. A.; March, C. J.; Kronheim, S. R.; Druck, T.; Cannizzaro, L. A.; Huebner, K.; Black, R. A. *Science* **1992**, *256*, 97.

(2) (a) Dinarello, C. A. *Blood* **1991**, *77*, 1627. (b) Dinarello, C. A.; Wolff. S. M. *N. Engl. J. Med.* **1993**, *328*, 106.

(3) (a) Koizumi, F.; Matsuda, Y.; Nakanishi, S. *J. Antibiot.* **2003**, *56*, 464. (b) Koizumi, F.; Ishiguro, H.; Ando, K.; Kondo, H.; Yoshida, M.; Matsuda, Y.; Nakanishi, S. *J. Antibiot.* **2003**, *56*, 603.

(4) Koizumi, F.; Takahashi, Y.; Ishiguro, H.; Tanaka, R.; Ohtaki, S.; Yoshida, M.; Nakanishi, S.; Ikeda, S. *Tetrahedron Lett.* **2004**, *45*, 7419.

(5) Kakeya, H.; Miyake, Y.; Shoji, M.; Kishida, S.; Hayashi, Y.; Kataoka, T.; Osada, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3743.

(6) Isolation: (a) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496. (b) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829. Total syntheses: (c) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192. (d) Shoji, M.; Kishida, S.; Takeda, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 9155. (e) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 7205. (f) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2004**, *69*, 1548. (g) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267. (h) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 3569. (i) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 3611.

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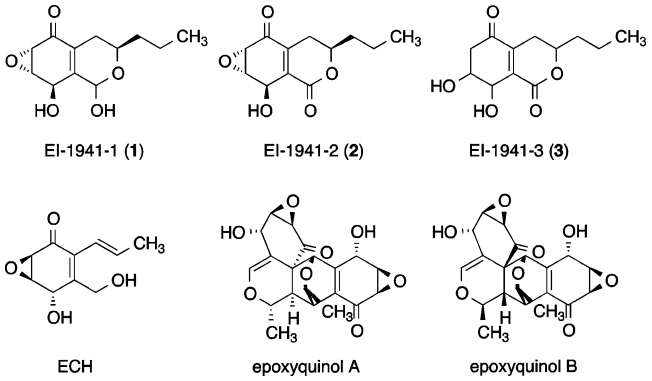
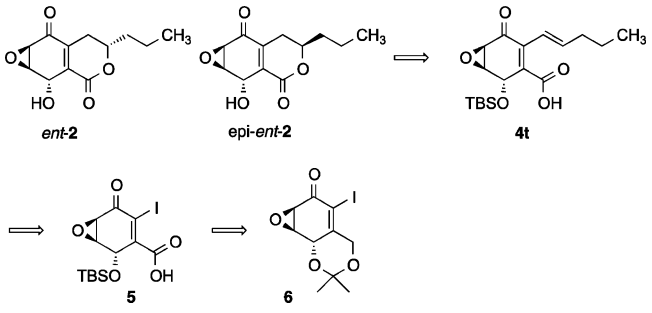


Figure 1. Structures of EI-1941-1, -2, -3, ECH, and epoxyquinols A and B.

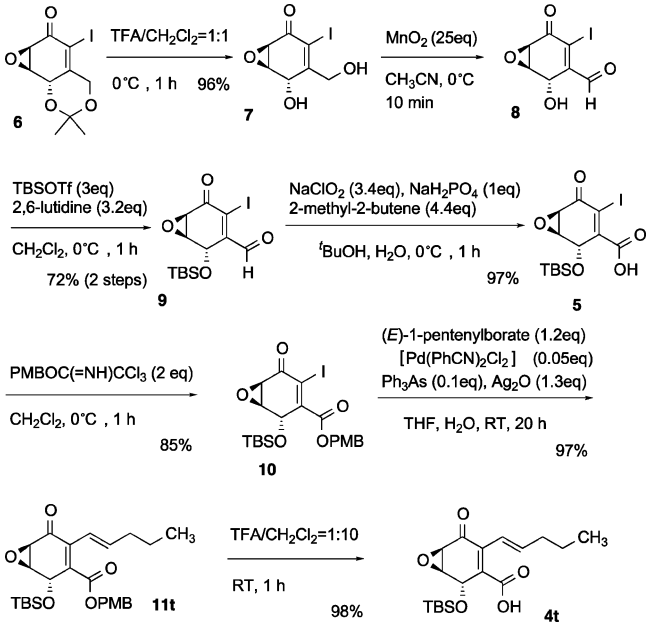
relative and absolute stereochemistries were not known. As most of the epoxyquinol natural products have a trans relationship between the epoxide and the 4-hydroxy group on the cyclohexenone,[7] a synthetic route by which the two diastereomers (EI-1941-2 and epi-EI-1941-2) can be generated with high optical purity was undertaken in order to determine the relative and absolute stereochemistries. EI-1941-2 and its epimer were to be prepared from diene carboxylic acid **4** via 6π-electrocyclization[8] or carboxy metalation via the 6-*endo* mode. **4** was to be synthesized from iodo compound **5** via the Suzuki coupling reaction, while we planned to produce **5** from the α-iodocyclohexanone derivative **6**, a key chiral intermediate in our total synthesis of epoxyquinols A and B, which is prepared by a sequence in which the Diels−Alder reaction of furan is one of the key steps.[6c,d]

Scheme 1. Retrosynthetic Analysis of *ent*-**2** and Epi-*ent*-**2**

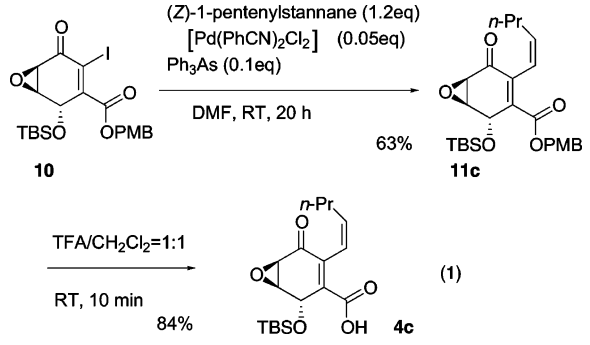


The synthesis starts from the chiral iodocyclohexenone **6**, easily prepared in a large quantity by our reported method[6c,d]

Scheme 2. Synthesis of **4t**



(Scheme 2). Cleavage of the acetonide on acid treatment gave diol **7**. Selective oxidation of the primary alcohol with excess MnO_2 in CH_3CN gave aldehyde **8**, the secondary alcohol of which was protected using TBSOTf and 2,6-lutidine, affording **9** in 72% yield over two steps. Oxidation of this aldehyde to the carboxylic acid was successfully performed under Kraus' conditions.[9] The carboxylic acid was protected as its *para*-methoxybenzyl ester **10** in 85% yield. Introduction of the side chain by a Suzuki coupling reaction with (*E*)-1-pentenylborate[10] and Ag_2O in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As[11] afforded **11t** in 97% yield. Acid treatment then gave carboxylic acid **4t** in excellent yield. The isomer with the (*Z*)-side chain **4c** was prepared in good yield by a Stille coupling reaction using (*Z*)-1-tributylpentenylstannane[12] in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As,[13] followed by the acid treatment (eq 1).



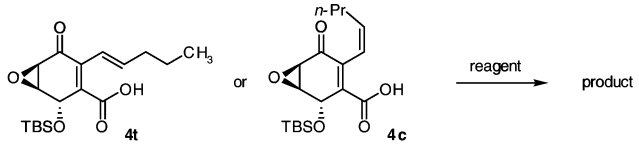
Next we examined the key cyclization of diene carboxylic acid **4t** via the 6-*endo* mode, and the results under several

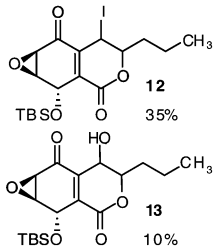
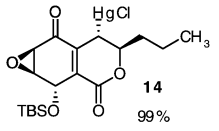
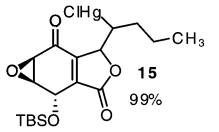
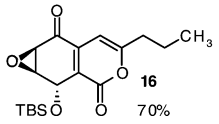
(7) (a) Terremutin: Miller, M. W. *Tetrahedron* **1968**, *24*, 4839. (b) Isoepoxydon: Nagasawa, H.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1303. (c) Eupenoxide: Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898. Liu, Z.; Jensen, P. R.; Fenical, W. *Phytochemistry* **2003**, *64*, 571. (d) Bromoxone: Higa, T.; Okuda, R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063. (e) Panepoxydon: Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214. (f) Cycloepoxydon: Gehrt, A.; Erkel, G.; Anke, H.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 259. Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 455.

(8) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

(9) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (b) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

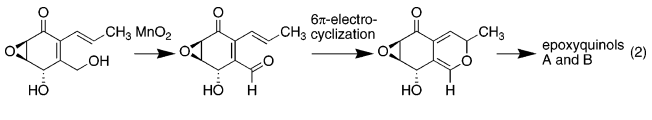
Table 1. Intramolecular Cyclization of **4t** and **4c**

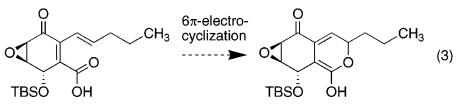


entry	reagent	SM[a]	Products
1	toluene, reflux, 12 h	**4 t**	NR[b]
2	TFA/CH_2Cl_2[c] RT, 1 h	**4 t**	NR[b]
3	NaH, THF, RT, 12 h	**4 t**	Decomposition of **4 t**
4	NIS, $NaHCO_3$ THF/H_2O, RT, 1 h	**4 t**	 **12** 35% **13** 10%
5	1) $Hg(OTf)_2$, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	**4 t**	 **14** 99%
6	1) $Hg(OTf)_2$, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	**4 c**	 **15** 99%
7	$Pd(PhCN)_2Cl_2$[d] *p*-benzoquinone THF, RT, 24 h	**4 t**	 **16** 70%

[a] Starting material. [b] No reaction. [c] TFA/CH_2Cl_2 = 1:10. [d] 10 mol % was employed.

reaction conditions are summarized in Table 1. In our previous syntheses of epoxyquinols A and B, the key step is a biomimetic cascade reaction composed of sequential oxidation, 6π-electrocyclization, and Diels−Alder dimerization[6c] (eq 2).



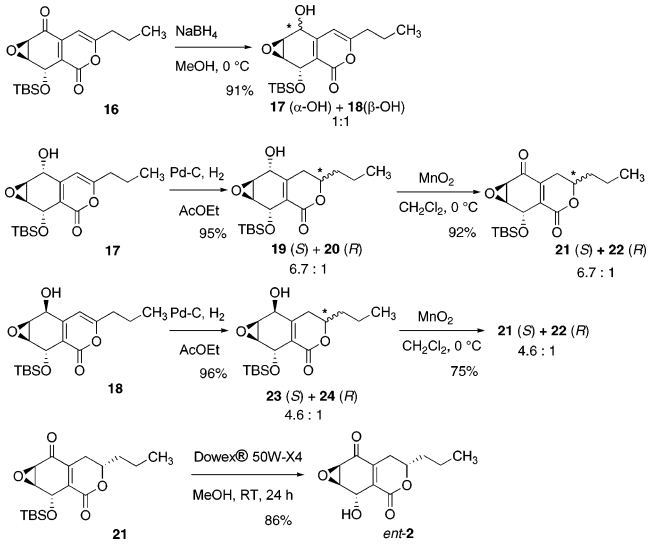


On the basis of the facile 6π-electrocyclization observed for a dienal,[6e,f] we expected that the same type of 6π-electrocyclization would proceed in the case of diene carboxylic acid **4t** or ester **11t** (eq 3). On the basis of this assumption, **4t** and **11t** were refluxed in toluene, but this led to complete recovery of the starting materials (entry 1). Acid catalyst does not promote the 6π-electrocyclization, and once again the starting material was completely recovered (entry 2). The conversion of carboxylic acid **4t** to its sodium carboxylate resulted in decomposition of the starting material (entry 3). As we had found that the 6π-electrocyclization of **4t** scarcely proceeds at all, intramolecular additions of the carboxylic acid onto the alkene activated with iodine or metal salts were examined, though diastereoselectivity and alternate reaction modes such as 6-*endo* or 5-*exo* are possible problems with this approach. In fact, iodolactonization proceeded in the 6-*endo* mode with low yield (entry 4), while in the case of carboxymercuration using $Hg(OTf)_2$,[14] the 6-*endo* cyclized product was obtained in excellent yield as a single isomer,[15] albeit with the incorrect side-chain relative stereochemistry for the natural product in the reaction of (*E*)-isomer **4t** (vide infra, entry 5), while the undesired 5-*exo* cyclization was observed in that of the (*Z*)-isomer **4c** (entry 6). Unlike these unsuccessful results, the 7,8-dihydro-6*H*-isochromen-1,5-dione structure **16** was formed when palladium(II) was used as a catalyst. That is, when **4t** was treated with *p*-benzoquinone and a catalytic amount of $Pd(PhCN)_2Cl_2$,[16] carboxypalladation proceeded, followed by the β-hydride elimination, affording **16** in 70% yield (entry 7).

The remaining steps are reduction of the double bond and deprotection. Hydrogenation of **16** under an H_2 atmosphere in the presence of Pd/C or $Pd(OH)_2$ did not proceed. As the keto group might be the cause of this reluctance to undergo hydrogenation, it was reduced with $NaBH_4$ in MeOH to afford alcohols **17** and **18** in 91% yield and equal amounts,[17] which were separated by column chromatography. Hydrogenation of α-alcohol **17** proceeded smoothly and stereoselectively, affording an inseparable mixture of **19** and **20** in excellent yield (95%) and with 6.7:1 diastereoselectivity, which was oxidized with MnO_2, affording ketones **21** and **22** in 92% yield in the same ratio. Though hydrogenation of β-alcohol **18** proceeded slowly, the reduced products **23** and **24** were obtained in 96% yield with the desired isomer predominating (4.6:1 diastereoselectivity). Oxidation of alcohols **23** and **24** with MnO_2 gave **21** and **22** in 75% yield

(10) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370.
(11) Ruel, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1997**, *75*, 69.
(12) Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4568.
(13) Farina, V.; Krishnamurphy, V.; Scott, W. *Org. React.* **1997**, 50, 1.
(14) (a) Nishizawa, M.; Takenaka, H.; Nishida, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581. (b) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett.* **1995**, 169. (c) Imagawa, H.; Shigaraki, T.; Suzuki, T.; Takao, T.; Yamada, H.; Sugihara, T.; Nishizawa, M. *Chem. Pharm. Bull.* **1998**, *46*, 1341. (d) Nishizawa, M.; Kashima, T.; Sakakibara, M.; Wakabayashi, A.; Takahashi, K.; Takao, T.; Imagawa, H.; Sugihara, T. *Heterocycles* **2000**, *54*, 629.
(15) Origin of the stereoselective formation of **14** is not clear at the moment.
(16) (a) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329. (b) Minami, T.; Nishimoto, A.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 9505.
(17) Stereochemistries of the alcohols **17** and **18** were determined by the modified MTPA method; see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Scheme 3. Total Synthesis of *ent*-EI-1941-2



in a 4.6:1 ratio, and these were easily separated by thin-layer chromatography.

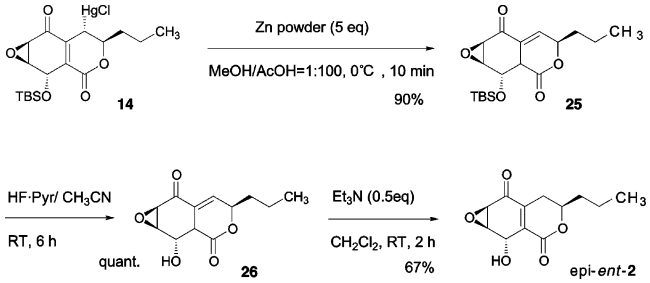
Removal of the TBS group of **21** afforded *ent*-EI-1941-2 in 86% yield. Synthetic *ent*-EI-1941-2 exhibited properties identical to those of the natural product except for the optical rotation, which was of opposite sign, indicating that the synthetic compound is the enantiomer of EI-1941-2.[3,4]

Epi-*ent*-EI-1941-2 was also prepared stereoselectively from carboxymercurated derivative **14**. Though conventional demercuration using Bu_3SnH in the presence of AIBN[18] did not work, affording **4t**, we found that the treatment of **14** with Zn powder in MeOH and AcOH[19] gave β,γ-unsaturated lactone **25**. After removal of the TBS group, to give alcohol **26**, treatment of this with a catalytic amount of amine isomerized the double bond to provide epi-*ent*-EI-1941-2 in 67% yield (Scheme 4).

(18) Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc*. **1970**, *92*, 6611.

(19) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1, pp 1276.

Scheme 4. Total Synthesis of Epi-*ent*-EI-1941-2



In summary, we have accomplished the first asymmetric total synthesis of *ent*-EI-1941-2 and epi-*ent*-EI-1941-2, starting from the chiral epoxy iodoquinone **6**, a key intermediate in our total synthesis of epoxyquinols A and B. A key step is the intramolecular, metal-mediated carboxylation of an alkene via the 6-*endo* cyclization mode, in which Pd(II) gave a 2*H*-pyran-2-one via β-hydride elimination, affording *ent*-EI-1941-2 after stereoselective hydrogenation, while $Hg(OTf)_2$ afforded a carboxymercurated product of side-chain relative stereochemistry opposite to that of the natural product, leading eventually to epi-*ent*-EI-1941-2 with high diastereoselectivity. We are currently investigating the synthesis of the natural enantiomer EI-1941-2, as well as that of EI-1941-1, the full accounts of which will be described shortly.

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

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