

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

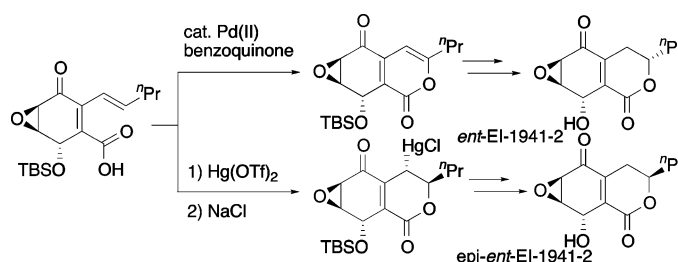
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ABSTRACT



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-1 β (IL-1 β) converting enzyme (ICE) is a cysteine protease that cleaves a biologically inactive 31 kDa precursor to biologically active IL-1 β ,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 IC₅₀ values of 0.086 and 0.006 μ M, 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 ECH⁵ 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

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(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.

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(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.

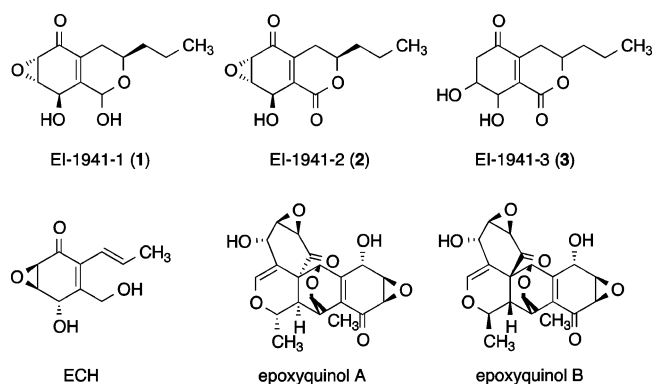
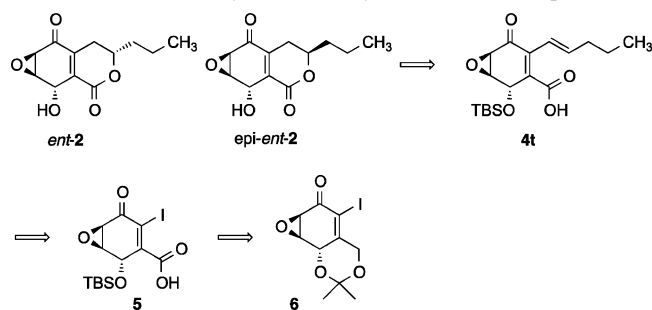


Figure 1. Structures of EI-1941-1, -2, -3, ECH, and epoxyquinols A and B.

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 -electrocyclization⁸ 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}

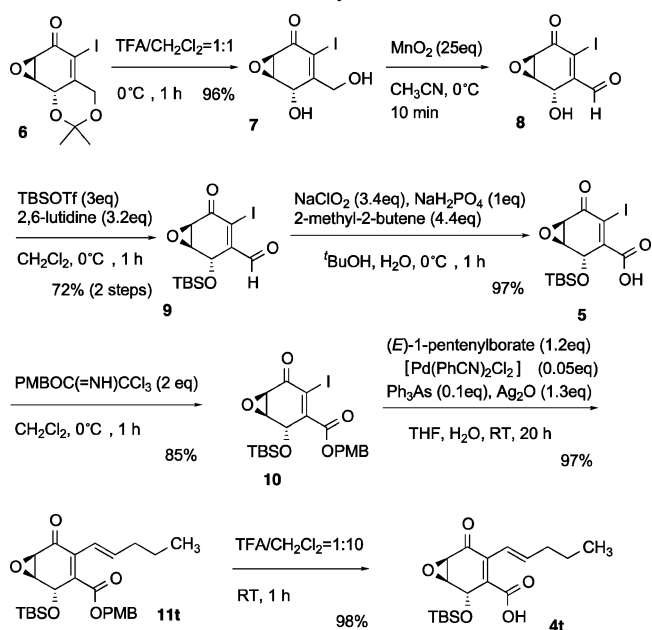
Scheme 1. Retrosynthetic Analysis of *ent*-2 and Epi-*ent*-2



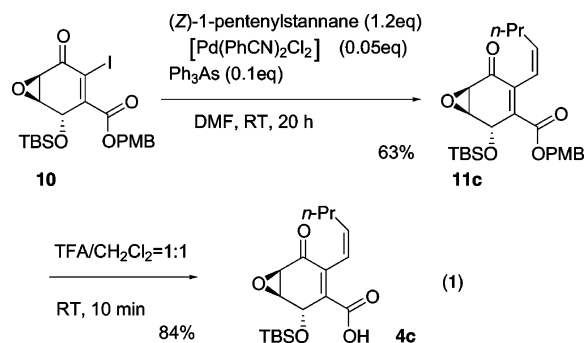
The synthesis starts from the chiral iodocyclohexenone **6**, easily prepared in a large quantity by our reported method^{6c,d}

(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.

Scheme 2. Synthesis of **4t**



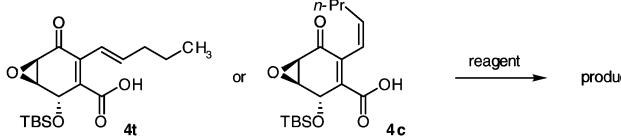
(Scheme 2). Cleavage of the acetonide on acid treatment gave diol **7**. Selective oxidation of the primary alcohol with excess MnO₂ in CH₃CN gave aldehyde **8**, the secondary alcohol of which was protected using TBSOTf and 2,6-lutidine, affording **9** in 72% yield over two steps. Oxidation of this 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-pentenylborate¹⁰ and Ag₂O in the presence of a catalytic amount of Pd(PhCN)₂Cl₂ and Ph₃As¹¹ 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-tributylpentenylstannane¹² in the presence of a catalytic amount of Pd(PhCN)₂Cl₂ and Ph₃As,¹³ followed by the acid treatment (eq 1).

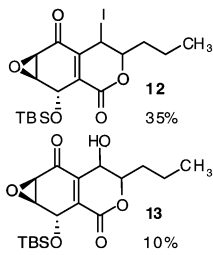
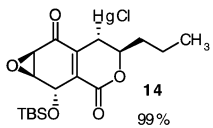
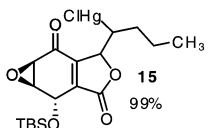
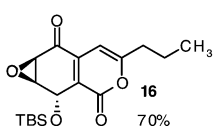


Next we examined the key cyclization of diene carboxylic acid **4t** via the *6-endo* mode, and the results under several

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

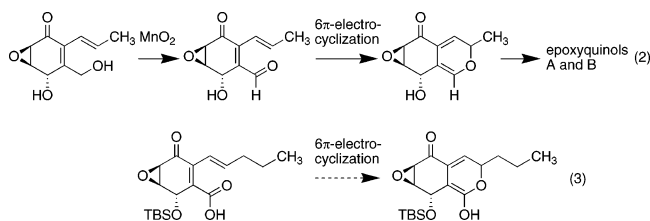
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Table 1. Intramolecular Cyclization of **4t** and **4c**


entry	reagent	SM ^a	Products
1	toluene, reflux, 12 h	4t	NR ^b
2	TFA/CH ₂ Cl ₂ ^c RT, 1 h	4t	NR ^b
3	NaH, THF, RT, 12 h	4t	Decomposition of 4t
4	NIS, NaHCO ₃ THF/H ₂ O, RT, 1 h	4t	
5	1) Hg(OTf) ₂ , MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	4t	
6	1) Hg(OTf) ₂ , MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	4c	
7	Pd(PhCN) ₂ Cl ₂ ^d <i>p</i> -benzoquinone THF, RT, 24 h	4t	

^a Starting material. ^b No reaction. ^c TFA/CH₂Cl₂ = 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, 6 π -electrocyclization, and Diels–Alder dimerization^{6c} (eq 2).



On the basis of the facile 6 π -electrocyclization observed for a dienal,^{6e,f} we expected that the same type of 6 π -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 6 π -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 6 π -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)₂Cl₂,¹⁶ 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 H₂ 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 NaBH₄ 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 MnO₂, 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 MnO₂ gave **21** and **22** in 75% yield

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(13) Farina, V.; Krishnamurphy, V.; Scott, W. *Org. React.* **1997**, *50*, 1.

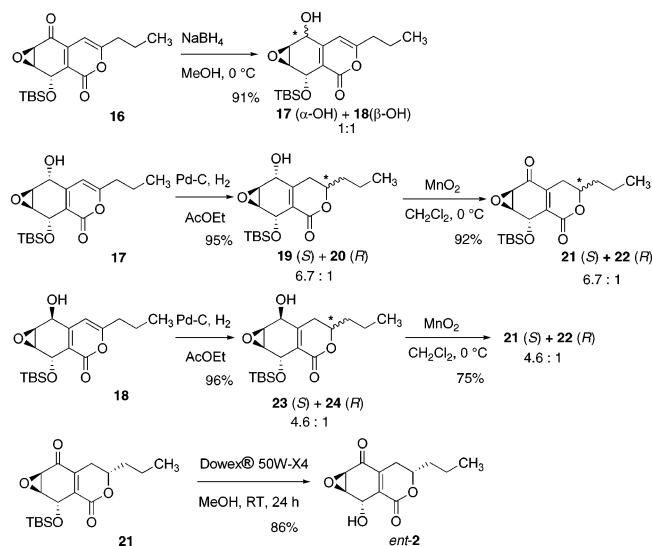
(14) (a) Nishizawa, M.; Takenaka, H.; Nishida, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581. (b) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett.* **1995**, 169. (c) Imagawa, H.; Shigaraki, T.; Suzuki, T.; Takao, T.; Yamada, H.; Sugihara, T.; Nishizawa, 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.

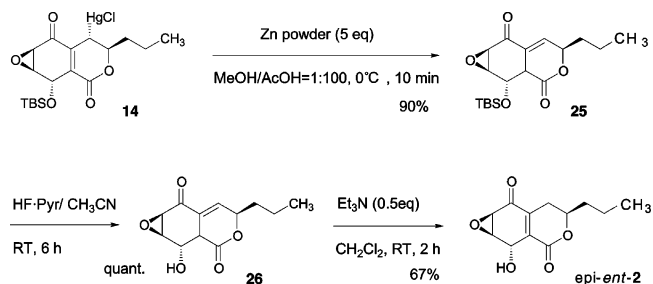
Removal of the TBS group of **21** afforded *ent*-EI-1941-2 in 86% yield. Synthetic *ent*-EI-1941-2 exhibited properties identical to those of the natural product except for the optical rotation, which was of opposite sign, indicating that the synthetic compound is the enantiomer of EI-1941-2.^{3,4}

Epi-*ent*-EI-1941-2 was also prepared stereoselectively from carboxymercurated derivative **14**. Though conventional demercuration using Bu₃SnH in the presence of AIBN¹⁸ did not work, affording **4t**, we found that the treatment of **14** with Zn powder in MeOH and AcOH¹⁹ 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).

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(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 ¹³C 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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