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Enantio- and Diastereoselective Total Synthesis of EI-1941−1, −2, and −3, Inhibitors of Interleukin-1β Converting Enzyme, and Biological Properties of Their Derivatives

Mitsuru Shoji,[†] Takao Uno,[†] Hideaki Kakeya,[‡] Rie Onose,[‡] Isamu Shiina,[§] Hiroyuki Osada,[‡] and Yujiro Hayashi*,[†]

Department of Industrial Chemistry, Faculty of Engineering, and Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan, and Antibiotics Laboratory, Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

hayashi@ci.kagu.tus.ac.jp

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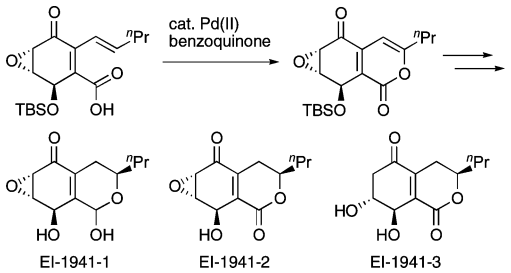

The first asymmetric total synthesis of EI-1941−1, −2, and −3, inhibitors of the interleukin-1β converting enzyme (ICE), has been accomplished, starting from a chiral epoxy iodoquinone **11**, a key intermediate in our total synthesis of epoxyquinols A and B. Despite a failure to synthesize the inhibitors by our postulated biosynthetic route, we were able to diastereoselectively synthesize them via an intramolecular carboxypalladation with the key steps being a 6-endo cyclization mode followed by β-hydride elimination. The investigation of the biological properties of EI-1941−1, −2, and −3 and their derivatives disclosed them to be potent and effective ICE inhibitors with less cytotoxicity than EI-1941−1 and −2 in a cultured cell system.

Introduction

Interleukin-1β (IL-1β) is an important mediator of pathogenesis of rheumatoid arthritis, septic shock, inflammation, and other physiological conditions.[1] IL-1β converting enzyme (ICE) is a cysteine protease, which cleaves a biologically inactive 31 kDa precursor to biologically active IL-1β.[2] IL-1β is released from macrophage-like cells in an inflammatory situation, and is the major form of IL-1 in diseases. ICE inhibitors have been shown to prevent inflammation in several acute models,[3] suggesting that ICE inhibitors would be useful as antiinflammatory drugs. Recently, Koizumi and coworkers 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, whereas the last is inactive at concentrations up to 10 μM in an in vitro system.[4] EI-1941−2 also has weak antimicrobial activities against Gram-positive

* Phone: +81 3-5228-8318. Fax: +81 3-5261-4631.
[†] Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science.
[§] Department of Applied Chemistry, Faculty of Science, Tokyo University of Science.
[‡] RIKEN.

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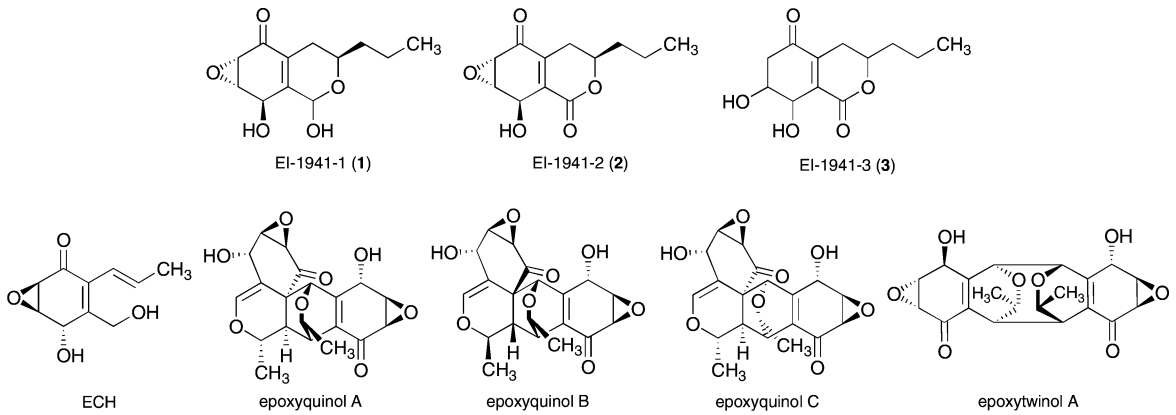

FIGURE 1. Natural products of epoxyquinol monomers and dimers.

bacteria, and moderate activity against *Proteus vulgaris*.[4] A more potent and effective ICE inhibitor would be desired, and EI-1941−1 and −2 would be suitable lead compounds for the study of the structure−activity relationship.

Structurally, EI-1941−1 and EI-1941−2 have an epoxyquinone core and a side chain. We have been interested in the synthesis and biology of epoxyquinone derivatives such as ECH ((2*R*,3*R*,4*S*)-2,3-epoxy-4-hydroxy-5-hydroxymethyl-6-(1*E*)-propenylcyclohex-5-en-1-one),[5] an inhibitor of Fas-mediated apoptosis, and its dimer, epoxyquinols A, B, and C, and epoxytwinol A, angiogenesis inhibitors.[6] At the time that we started this project, the relative and absolute stereochemistries of EI-1941−1, −2, and −3 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] work on 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 stereochemistries. As for the absolute stereochemistry, with the structural similarity between EI-1941 and ECH, we tried to synthesize the (1*R*,5*S*,6*R*)-1,6-epoxy-5-hydroxycyclohexenone derivative as our first target.

When we had nearly finished the synthesis of the targeted isomer of EI-1941−2 and its epimer, the absolute and relative stereochemistries of EI-1941−1 and −2 were reported (see Figure 1),[8] whereas those of EI-1941−3 were not determined because of its low availability from the fermentation broth. Those determinations were made on the basis of the crystallographic analysis of the *p*-bromobenzoyl ester of EI-1941−2 and the chemical correlation between EI-1941−1 and −2. These results indicate that the compounds we have synthesized are opposite enantiomers of the natural EI-1941−2 and its epimer, which was communicated in a previous letter.[9]

As for the biosynthesis, we postulated the following path: Oxidation of alcohol **4** would afford aldehyde **5**, from which 6π-electrocyclization[10] proceeds to generate 2*H*-pyran **6**. Hydration and isomerization would afford EI-1941−1, the oxidation of which would provide EI-1941−2 (eq 1). Another possible path involves the oxidation of alcohol **4** to carboxylic acid **7**, from which 6π-electrocyclization proceeds to generate hydroxy-2*H*-pyran **8** (eq 2). Isomerization would afford EI-1941−2, the reduction of which would provide EI-1941−1. Similar 2*H*-pyran **10** is a key intermediate of our biomimetic total synthesis of epoxyquinols A, B, and C, and epoxytwinol A, which was generated by the oxidation of ECH followed by the 6π-electrocyclization.[6c,f,g]

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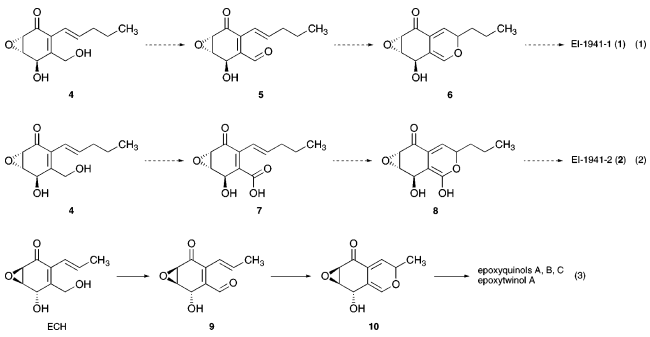
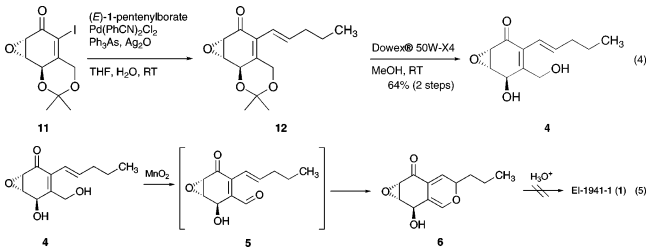


In this full paper we will describe the highly stereoselective, asymmetric total synthesis of the natural enantiomers of EI-1941−1, −2, and −3 in a full account, including an attempted total synthesis based on a biomimetic route with the theoretical calculation of 6π-electrocyclization of dienecarboxylic acid derivatives. We also describe the biological properties of EI-1941−1, −2, and −3 and their derivatives, including the finding of a more superior ICE inhibitor that is less cytotoxic than EI-1941−1 and −2.

Results and Discussion

Synthetic Study Based on Our Postulated Biosynthetic Pathway. As described in the Introduction, EI-1941−1 would be generated by the hydration and isomerization of 2*H*-pyran **6**, and we already found that the similar 2*H*-pyran **10**, generated by the oxidation of ECH, dimerized gradually under neat conditions or in a rather condensed solution (eq 3).[6c,f,g] We thought the vinyl ether moiety of **6** would react with H_2O before it dimerizes when 2*H*-pyran **6** was treated with acid in a dilute solution. Epoxycyclohexenol **4**, the starting material, was synthesized from the chiral iodocyclohexenone **11**,[6c,d,g] an enantiomer of the intermediate of our total synthesis of epoxyquinols, by the Suzuki coupling reaction with (*E*)-1-pentenylborate[11] and Ag_2O in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As,[12] followed by cleavage of the acetonide on acid treatment (eq 4). 2*H*-Pyran derivative **6** was isolated after the oxidation of alcohol **4** with MnO_2, followed by 6π-electrocyclization. Though 2*H*-pyran **6** was treated with several acids such as PPTS, $TsOH\cdot H_2O$, and CF_3CO_2H in several dilute aqueous solvents, a complex mixture was obtained without isolation of the desired product (eq 5), which prompted us to examine the 6π-electrocyclization of a diene carboxylic acid derivative.

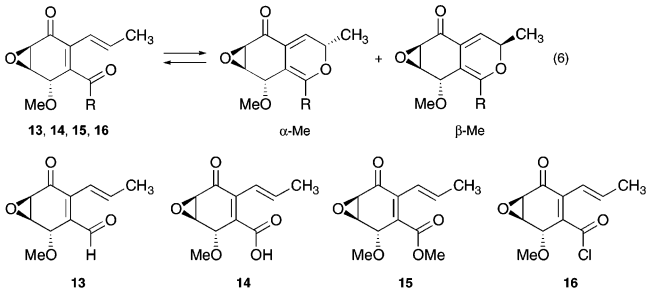


Despite the facile 6π-electrocyclization of dienal **5**, 6π-electrocyclization has generally been regarded as a difficult reaction.[10] According to the recent theoretical calculation of 2,4-pentadienal, a simple dienal, 6π-electrocyclization is an equilibrium that shifts to the starting material, and 2*H*-pyran is more energetically unstable than the parent aldehyde with a TS energy of 3.44 kcal/mol versus 21.52 kcal/mol.[13] In the case of ECH, however, an electron-withdrawing keto group on cyclohexane reduces the TS energy with the stabilization of the 2*H*-pyran intermediate **10** (eq 3).[6f] As 6π-oxa-electrocyclization has been investigated only for the diene-aldehydes without a systematic study of that for diene-carboxylic acids or esters, the theoretical calculations for the substrates having a propenyl side chain and functional groups such as aldehyde **13**, carboxylic acid **14**, methyl ester **15**, and acid chloride **16** were performed at the B3LYP/6-31G* level with the program package *TITAN* 1.0.5 including DFT engine Jaguar 3.5.042.2.[14] For all the transition-state searches, vibrational frequencies were computed after completion of the optimization from analytic second derivatives.

TABLE 1. Calculated TS Energy and Relative Energy between Diene Carbonyl Compound and α- and *β*-Methyl 2*H*-Pyran Derivatives

entry	starting material	TS energy (kcal mol^{-1})	relative energy[a] (kcal mol^{-1})	isomer[b]
1	**13**	17.74	−4.16	α
2	**13**	15.50	−4.18	*β*
3	**14**	25.34	+5.78	α
4	**14**	8.83	+6.26	*β*
5	**15**	25.65	+9.24	α
6	**15**	10.23	+8.66	*β*
7	**16**	22.50	+1. 73	α
8	**16**	9.46	+1. 58	*β*

[a] The values are relative energies between the diene carbonyl compound and 2*H*-pyran in the 6π-electrocyclization. [b] α indicates the α-methyl isomer, whereas *β* indicates the *β*-methyl isomer.



There are two isomers for the 6π-oxa-electrocyclized products such as α- and *β*-methyl derivatives (eq 6). The transition-state energies for both α- and *β*-methyl-2*H*-pyran derivatives, and the relative energies between diene carbonyl derivatives and 2*H*-pyran derivatives, are calculated with the results summarized in Table 1. We have experimentally demonstrated the facile electrocyclization of diene aldehyde **13**, which is supported by the calculation showing that the 6π-electrocyclized product is more stable than the starting material with the low transition-state energies of 17.74 and 15.50 kcal/mol to α- and *β*-methyl 2*H*-pyran derivatives, respectively (en-

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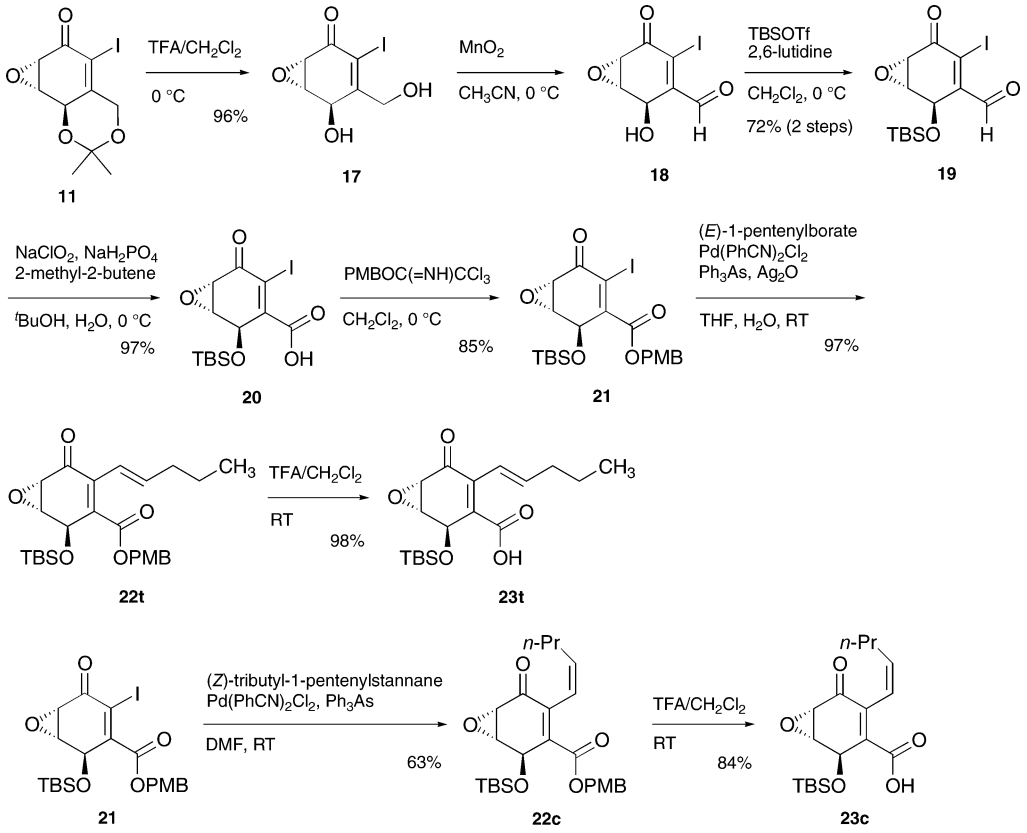
SCHEME 1. Synthesis of 23t and 23c



tries 1, 2). Diene carboxylic acid derivatives **14**, **15**, and **16** showed results different from those of diene aldehyde **13**. 6π-Electrocyclization might proceed, judging from the low transition-state energy to the β-methyl isomer, whereas that to the α-methyl isomer is too high for the 6π-electrocyclization to proceed at room temperature. As for the relative energies between the starting materials and the 2*H*-pyran derivatives, 2*H*-pyran derivatives are very unstable except for the acid chloride **16**, indicating that the equilibrium shifts mostly to the starting material, and the concentration of the 2*H*-pyran derivatives would be quite low. Even in the case of acid chloride **16**, though the 2*H*-pyran derivative is slightly more unstable (1.58 kcal/mol) than the starting material, the equilibrium also shifts to the starting material with the low concentration of 2*H*-pyran.

Synthesis of Carboxylic Acid Derivatives. With the calculation results in hand, we examined the 6π-oxa-electrocyclization of several derivatives. Before describing the results of 6π-oxa-electrocyclization, we will briefly mention the synthesis of carboxylic acid **23t** (see Scheme 1). Cleavage of the acetonide of the chiral iodocyclohexenone **11** with an acid treatment gave diol **17**. Selective oxidation of the primary alcohol with excess MnO_2 in CH_3CN gave aldehyde **18**; the secondary alcohol was protected by the use of TBSOTf and 2,6-lutidine, affording **19** in 72% yield over two steps. Oxidation of this aldehyde to the carboxylic acid was successfully performed under Kraus' conditions.[15] The carboxylic acid was protected as its *p*-methoxybenzyl ester **21** by the reaction with 4-methoxybenzyl trichloroacetimidate[16] in 85% yield. The introduction of a side chain by the Suzuki coupling reaction with (*E*)-1-pentenylborate and Ag_2O in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As afforded **22t** in 97% yield. Acid treatment then gave carboxylic acid **23t** in excellent yield. The isomer with the *Z* side chain, **23c**, was prepared in good yield by the Stille coupling reaction using (*Z*)-tributyl-1-pentenylstannane in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As, followed by the acid treatment.

With the starting materials in hand, we investigated the 6π-electrocyclization of dienecarboxylic acid. No reaction proceeded even at reflux in toluene, with the recovery of the starting materials in the cases of carboxylic acid **23t** and ester **22t**. When acid chloride generated from carboxylic acid **23t** with oxalyl chloride and a catalytic amount of DMF was gently heated to 60 °C in $CDCl_3$, a complex mixture was obtained. Only decomposition occurred when acid chloride was treated with $AlCl_3$ to generate the acylium ion.

As all our trials using 6π-electrocyclization as a key step were in vain, we pursued another synthetic route using intramolecular carboxymetalation.

Intramolecular Carboxymetalation. Intramolecular addition of the carboxylic acid onto the alkene activated with iodine or metal salts was examined, though diastereoselectivity and alternate reaction modes such as 6-endo or 5-exo are possible problems with this approach (Table 2). In fact, iodolactonization proceeded

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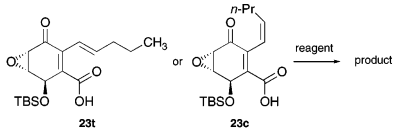
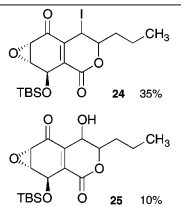
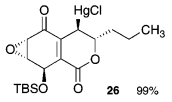
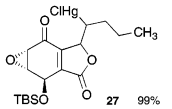
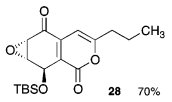
TABLE 2. Intramolecular Cyclization of 23t and 23c



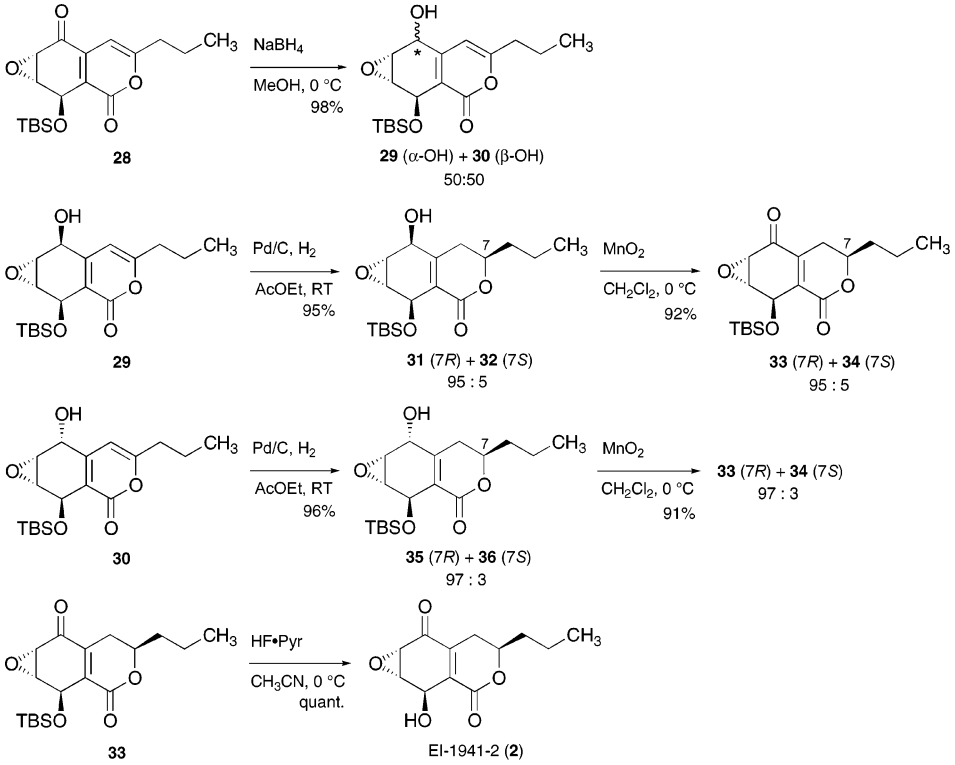
entry	reagent	SM[a]	products
1	NIS, $NaHCO_3$ THF/H_2O, RT, 1 h	**23t**	 **24** 35% **25** 10%
2	1) $Hg(OTf)_2$, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	**23t**	 **26** 99%
3	1) $Hg(OTf)_2$, MS4A, EtCN/MeCN -78 °C, 3 min 2) aq. NaCl	**23c**	 **27** 99%
4	$Pd(PhCN)_2Cl_2$[b] *p*-benzoquinone THF, RT, 24 h	**23t**	 **28** 70%

[a] Starting material. [b] Ten mole percent was employed.

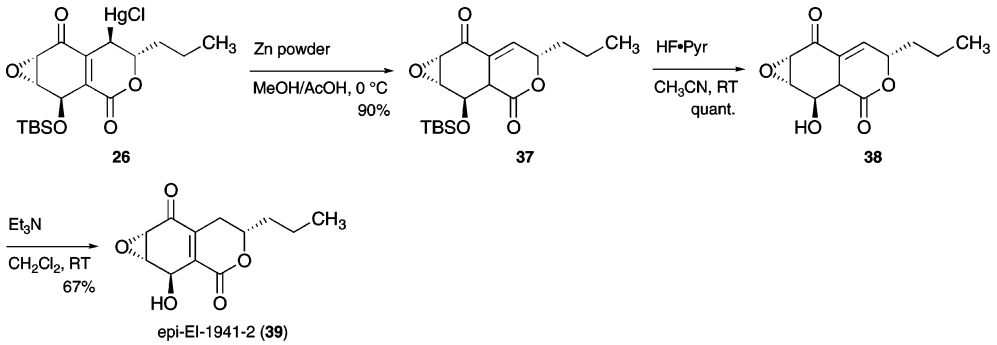
in the 6-endo mode with low yield (entry 1), whereas in the case of carboxymercuration using $Hg(OTf)_2$,[17] the 6-endo cyclized product was obtained in excellent yield as a single isomer, albeit with the incorrect side-chain relative stereochemistry at C7 in the reaction of *E* isomer **23t** (vide infra, entry 2). Undesired 5-exo cyclization was observed in that of the *Z* isomer **23c** (entry 3). Unlike these unsuccessful results, the 7,8-dihydro-6*H*-isochromen-1,5-dione structure **28** was formed when palladium(II) was used as a catalyst. That is, when **23t** was treated with *p*-benzoquinone and a catalytic amount of $Pd(PhCN)_2Cl_2$,[18] carboxypalladation proceeded, followed by the *β*-hydride elimination, affording **28** in 70% yield (entry 4).

The remaining steps are reduction of the double bond and deprotection (see Scheme 2). Hydrogenation of **28** 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 **29** and **30** in 98% yield and equal amounts, which were separated by column chromatography. The relative stereochemistry is determined by the modified MTPA-ester method[19] of **29**. Hydrogenation of α-alcohol **29** proceeded smoothly and stereoselectively, affording an inseparable mixture of **31** and **32** in excellent yield (95%) and with high diastereoselectivity (95:5). It should be noted that the concentration is important for the diastereoselectivity. Whereas excellent diastereoselectivity (95:5) was obtained at 0.01 M, lower selectivity (87:13) was observed at a higher concentration (0.1 M).[9,20] The mixture of **31** and **32** was oxidized with MnO_2, affording ketones **33** and **34** in 92% yield (95:5), which were easily separated by thin-layer chromatography (TLC). Though hydrogenation of *β*-alcohol **30** proceeded slowly, the reduced products **35** and **36** were obtained in 96% yield with the desired isomer stereoselectivity (97:3). In this hydrogenation, the concentration is also crucial. Excellent diastereoselectiv-

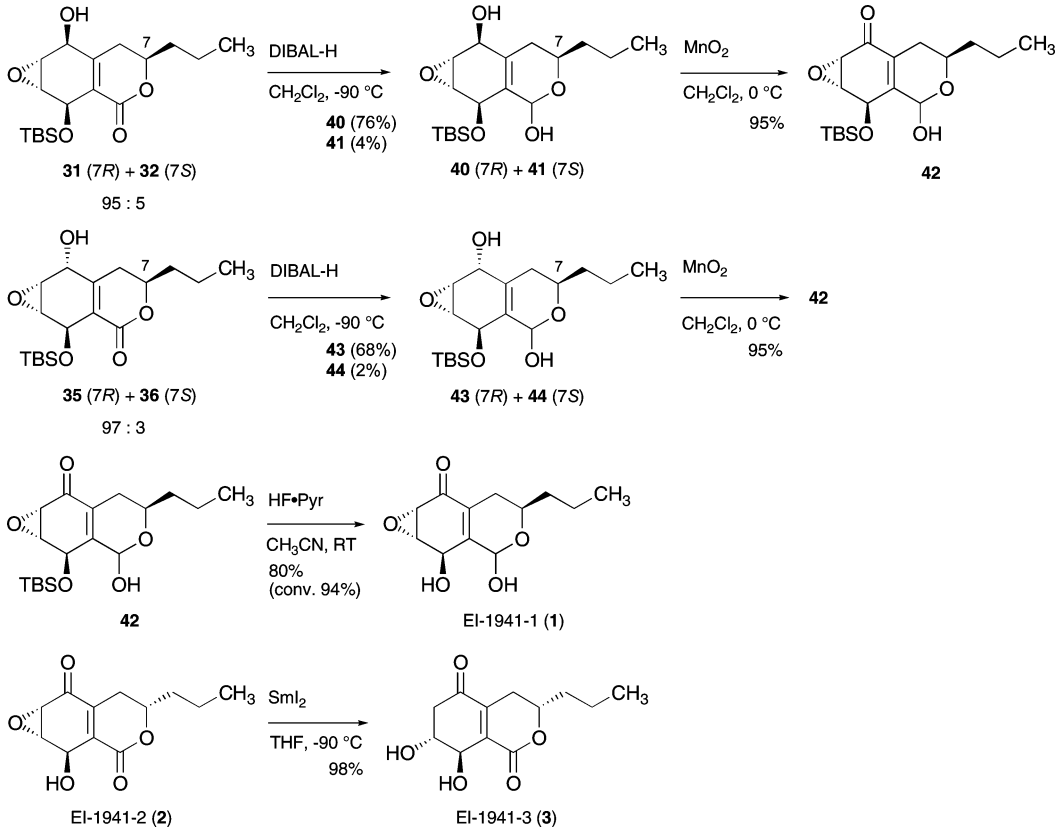
SCHEME 2. Synthesis of EI-1941−2 (2)



SCHEME 3. Synthesis of Epi-EI-1941−2 (39)



SCHEME 4. Synthesis of EI-1941−1 (1) and EI-1941−3 (3)



ity (97:3) is observed at low concentration (0.01 M) in contrast to the lower selectivity (83:17) at higher concentration (0.1 M).[9] Oxidation of alcohols **35** and **36** with MnO_2 gave **33** and **34** in 91% yield in a 97:3 ratio, and these were separated by TLC.

Removal of the TBS group of **33** afforded EI-1941−2 (**2**) quantitatively. Synthetic EI-1941−2 (**2**) exhibited properties identical to those of the natural product,[4b,8] including the optical rotation.

epi-EI-1941−2 was also prepared stereoselectively from carboxymercurated derivative **26**. Though conventional demercuration using Bu_3SnH in the presence of AIBN[21] did not work, affording **23t**, we found that the treatment of **26** with Zn powder in MeOH and AcOH[22] gave β,γ-unsaturated lactone **37**. After removal of the TBS group, treatment with a catalytic amount of amine isomerized the double bond to provide epi-EI-1941−2 (**39**) in 67% yield (Scheme 3).

Synthesis of EI-1941−1 and −3. EI-1941−1 was synthesized (see Scheme 4) from α-alcohol **31** and β-alcohol **35**, the intermediates of EI-1941−2, as follows: When α-alcohols **31** and **32** (**31**:**32** = 95:5) were treated with DIBAL-H in CH_2Cl_2 at low temperature (−90 °C),

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(18) (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.

(19) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.

(20) The reason for the effect of the concentration on the diastereoselectivity is not clear.

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

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

TABLE 3. Summary of IC_{50} Values of Test Compounds on IL-1β Secretion from LPS-Stimulated THP-1 Cells and on Cell Viability of THP-1 Cells

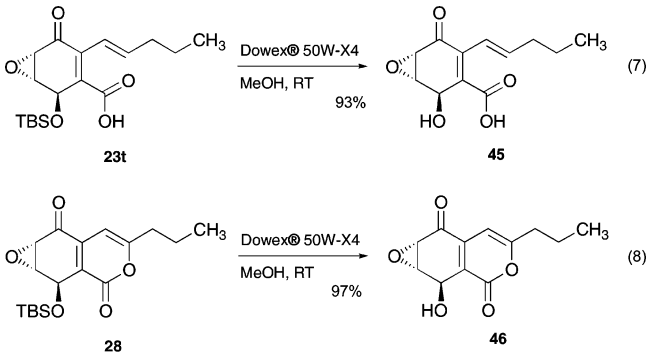
compound	IC_{50} values[a] on IL-1β secretion (μM)	IC_{50} values[b] on cell viability (μM)
EI-1941−1 (**1**)	56	>100
EI-1941−2 (**2**)	15	40
ent-**2**	10	68
EI-1941−3 (**3**)	>100	>100
45	>100	>100
ent-**45**	74	>100
46	14	20
ent-**46**	10	30

[a] Concentration of 50% inhibitory activity on LPS-stimulated IL-1β secretion. [b] Concentration of 50% inhibitory activity on cell viability.

lactone was reduced stereoselectively to lactols **40** and **41**, which were separated by TLC (76% **40**, 4% **41**). Oxidation of **40** with MnO_2 gave ketone **42** in excellent yield (95%). β-Alcohols **35** and **36** were also reduced with DIBAL-H to afford lactols **43** and **44**, which were separated by TLC (68% **43**, 2% **44**). Oxidation of **43** gave the same ketone **42** in 95% yield. Deprotection with HF·pyridine afforded EI-1941−1 (**1**) in good yield.

Reduction of the epoxide with SmI_2[23] at low temperature (−90 °C) cleanly converted EI-1941−2 into EI-1941−3 nearly quantitatively. Synthetic EI-1941−1, −2, and −3 exhibited properties identical to those of the natural products, including the optical rotation, which indicate that natural enantiomers were successfully synthesized. Comparison of the optical rotation of EI-1941−3 (synthetic **3**: $[\alpha]^{30}_D$ −88.7, natural **3**:[4b,8] $[\alpha]^{23}_D$ −87.5) determined its absolute stereochemistry.

Biological Evaluation. We evaluated the effects of EI-1941−1 (**1**), −2 (**2**), and −3 (**3**) and their derivatives on the extracellular release of IL-1β from THP-1 cells and cell viability in THP-1 cells, with the results summarized in Table 3 and Figure 2. The derivatives examined are *ent*-EI-1941−2 (*ent*-**2**), hydroxy carboxylic acid **45** and its enantiomer *ent*-**45**, and tetrahydro isocoumarin derivative **46** and its enantiomer *ent*-**46**. Hydroxy carboxylic acid **45** and tetrahydro isocoumarin derivative **46** were easily prepared from **23t** and **28**, respectively, by removal of the TBS group on acid treatment in MeOH, in good yields (eqs 7 and 8).



Compounds **1** and **2** inhibited IL-1β secretion in a dose-dependent manner; IC_{50} values of **1** and **2** in our assay system were 56 and 15 μM, respectively. IC_{50} values of **1** and **2** on cell viability were >100 and 40 μM, respectively. Compound **3**, which has been reported as an inactive compound in an in vitro system,[4] was inactive in THP-1 cells. These results indicate that an epoxide ring in **2** is essential for exhibiting the biological activities of **2**. Moreover, IC_{50} values of *ent*-**2** on IL-1β secretion and cell viability were 10 and 68 μM, respectively, which was a most effective derivative because the differences in IC_{50} values against IL-1β secretion and cell viability were greatly significant. The inhibition of IL-1β secretion by hydroxy carboxylic acids **45** and *ent*-**45** was weak (IC_{50} values of >100 and 74 μM, respectively), suggesting that a three-fused-ring system was important for the biological activity. Moreover, IC_{50} values of tetrahydro isocoumarin derivatives **46** and *ent*-**46** on IL-1β secretion were 14 and 10 μM, respectively. However, these two compounds **46** and *ent*-**46** also affected the cell viability at IC_{50} values of 20 and 30 μM, respectively. These results indicate that the enantiomer of EI-1941−2 (*ent*-**2**) is a more potent and effective ICE inhibitor than natural EI-1941−2 in a cultured cell system.

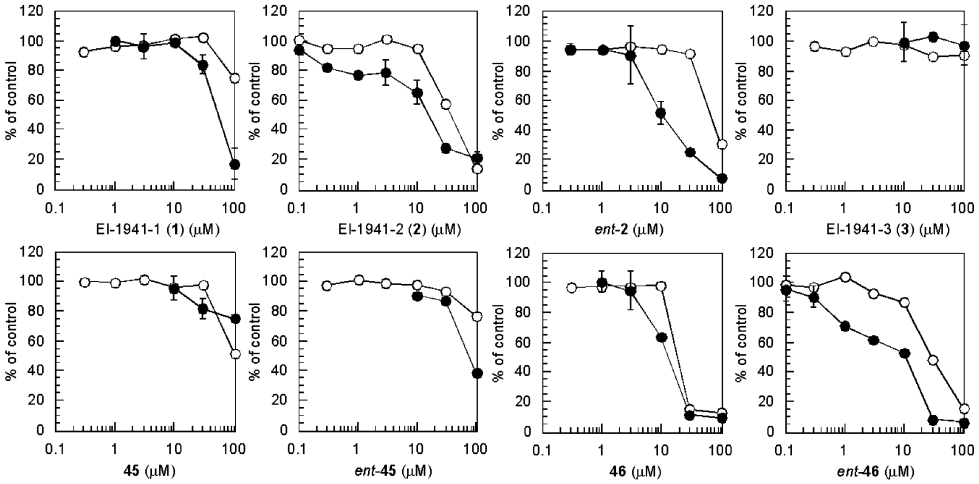


FIGURE 2. Effect of EI-1941−1 (**1**), −2 (**2**), and −3 (**3**) and their derivatives on IL-1β secretion from LPS-stimulated THP-1 cells and on cell viability of THP-1 cells. Symbols indicate IL-1β secretion (closed circle) and percentage of viable cells (open circle).

Conclusion

We have accomplished the first asymmetric total synthesis of EI-1941−1, −2, and −3, starting from the chiral epoxy iodoquinone **11**, 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 6-endo cyclization, in which Pd(II) gave 2*H*-pyran-2-one via *β*-hydride elimination, affording EI-1941−2 after stereoselective hydrogenation. $Hg(OTf)_2$ afforded a carboxymercurated product of a side-chain relative stereochemistry opposite to that of the natural product, leading eventually to epi-EI-1941−2 with high diastereoselectivity. EI-1941−1 was synthesized stereoselectively from the intermediate of EI-1941−2, whereas EI-1941−3 was synthesized in one step from EI-1941−2. By using this asymmetric total synthesis, we determined the absolute stereochemistry of EI-1941−3. The structure−activity relationship of EI-1941−1, −2, and −3 and their synthetic derivatives revealed that an enantiomer of EI-1941−2 is a more potent ICE inhibitor than EI-1941−2, as it is less cytotoxic.

Experimental Section

(1*R*,5*S*,6*R*)-5-Hydroxy-4-hydroxymethyl-3-iodo-7-oxabicyclo[4.1.0]hept-3-ene-2-one (**17**). To a solution of acetonide **11** (100 mg, 0.311 mmol) in CH_2Cl_2 (3.1 mL) was added trifluoroacetic acid (3.1 mL) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced preaaure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:1) to afford diol **18** (84 mg, 96%) as a yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ 3.63 (1H, dd, J = 1.6, 3.6 Hz), 3.85 (1H, dd, J = 1.4, 3.6 Hz), 4.44 (2H, d, J = 3.2 Hz), 4.98 (1H, br-s); ^{13}C NMR (100 MHz, CD_3OD) δ 52.5, 57.4, 64.6, 69.6, 102.1, 163.2, 189.8; FT-IR (neat) ν 3392, 1682, 1591, 1273, 1228, 1080, 1051, 931, 856, 758, 525 cm^{-1}; HRMS (FAB) $[M + Na]^+$ calcd for $[C_7H_7IO_4 + Na]^+$ 304.9287, found 304.9301; $[\alpha]^{23}_D$ −31.7 (*c* 0.212, MeOH).

(1*S*,2*S*,6*R*)-2-(*tert*-Butyldimethylsiloxy)-4-iodo-5-oxo-7-oxabicyclo[4.1.0]hept-3-ene-3-carbaldehyde (**19**). To a solution of diol **17** (81 mg, 0.287 mmol) in CH_3CN (2.9 mL) was added MnO_2 (624 mg, 7.18 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 10 min at that temperature. The reaction mixture was filtered through a pad of Celite, and concentrated in vacuo. The residue was filtered through a pad of silica gel (AcOEt/hexane = 1:3) to afford aldehyde **18**, and the crude product was used for the next reaction without further purification. To a solution of aldehyde **18** (170 mg, 0.606 mmol) and TBSOTf (481 mg, 1.82 mmol) in CH_2Cl_2 (6.1 mL) was added 2,6-lutidine (0.23 mL, 1.94 mmol) at 0 °C, and the mixture was stirred for 1 h under an argon atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl, and diluted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:10) to afford siloxy aldehyde **19** (170 mg, 72%, 2 steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.22 (3H, s), 0.82 (9H, s), 3.73 (2H, d, J = 1.2 Hz), 5.21 (1H, br-s), 9.79 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 18.0, 25.6, 51.8, 56.2, 63.5, 117.9, 148.2, 190.6, 197.0; FT-IR (neat) ν 2954, 2929, 2858, 1705, 1689, 1581, 1471, 1340, 1255, 1167, 1049, 839, 781, 511 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{13}H_{20}IO_4Si$ 395.0176, found 395.0178; $[\alpha]^{22}_D$ −3.2 (*c* 0.56, MeOH).

(23) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.

(1*S*,2*S*,6*R*)-2-(*tert*-Butyldimethylsiloxy)-4-iodo-5-oxo-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic Acid (**20**). To a solution of siloxy aldehyde **19** (100 mg, 0.25 mmol), NaH_2PO_4 (40 mg, 0.25 mmol), and 2-methyl-2-butene (0.1 mL, 1.11 mmol) in *tert*-BuOH (1.8 mL) and H_2O (0.5 mL) was added $NaClO_2$ (78 mg, 0.86 mmol) at 0 °C, and the reaction mixture was stirred for 1 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:10) to afford carboxylic acid **20** (104 mg, 97%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.14 (3H, s), 0.84 (9H, s), 3.62 (1H, br-*d*, J = 3.0 Hz), 3.69 (1H, br-s), 3.79 (1H, br-s), 5.18 (1H, br-s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.56, 18.0, 25.6, 51.0, 56.8, 66.7, 103.2, 152.9, 170.8, 189.1; FT-IR (neat) ν 3199, 2954, 2929, 2858, 1689, 1604, 1389, 1259, 839, 781, 756, 501 cm^{-1}; HRMS (FAB) $[M + Na]^+$ calcd for $[C_{13}H_{19}IO_5Si + Na]^+$ 432.9944, found 432.9938; $[\alpha]^{23}_D$ +26.1 (*c* 0.12, MeOH).

(1*S*,2*S*,6*R*)-2-(*tert*-Butyldimethylsiloxy)-4-iodo-5-oxo-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic Acid 4-Methoxybenzyl Ester (**21**). To a solution of carboxylic acid **20** (50 mg, 0.12 mmol) in CH_2Cl_2 was added $PMBOC(=NH)CCl_3$ (102 mg, 0.24 mmol) at 0 °C, and the reaction mixture was stirred for 1 h under an argon atmosphere. The reaction mixture was quenched with pH 7.0 phosphate buffer, and diluted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:3−1:10) to afford PMB ester **21** (55 mg, 85%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.11 (3H, s), 0.83 (9H, s), 3.62 (1H, dd, J = 1.3, 3.7 Hz), 3.64 (1H, dd, J = 1.0, 3.7 Hz), 3.79 (3H, s), 5.04 (1H, m), 5.21 (2H, dd, J = 11.7, 18.4 Hz), 6.87 (2H, m), 7.35 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.6, 17.9, 25.4, 50.9, 55,3, 57.0, 66.8, 68.2, 103.8, 114.0, 126.3, 131.0, 151.3, 160.1, 166.0, 188.6; FT-IR (neat) ν 2954, 2858, 1699, 1516, 1241, 1107, 1034, 841, 781 cm^{-1}; HRMS (FAB) $[M]^+$ calcd for $C_{21}H_{27}IO_6Si$ 530.0622, found 530.0637; $[\alpha]^{22}_D$ +19.9 (*c* 0.158, MeOH).

(1*S*,2*S*,6*R*)-2-(*tert*-Butyldimethylsiloxy)-5-oxo-4-pentyl-7-oxa-bicyclo[4.1.0]hept-3-ene-3-carboxylic Acid 4-Methoxybenzyl Ester (**22t**). To a solution of PMB ester **21** (48 mg, 0.09 mmol), (*E*)-1-pentenylborate (16 mg, 0.136 mmol), Ag_2O (33.6 mg, 0.145 mmol), and Ph_3As (2.8 mg, 0.009 mmol) in $THF.H_2O$ (8:1, 0.45 mL) was added $Pd(PhCN)_2Cl_2$ (1.7 mg, 0.0045 mmol) at room temperature in the dark, and the reaction mixture was stirred for 14 h under an argon atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl, and stirred for 30 min at that temperature. The reaction mixture was filtered through a pad of Celite, and the organic materials were extracted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:5∼1:20) to afford dienone **22t** (42 mg, 97%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.09 (3H, s), 0.82 (9H, s), 0.84 (3H, t, J = 7.3 Hz), 1.32 (2H, sextet, J = 7.3 Hz), 1.90−2.02 (2H, m), 3.54 (1H, d, J = 4.0 Hz), 3.60 (1H, dd, J = 1.9, 4.0 Hz), 3.79 (3H, s), 5.10 (2H, d, J = 11.8 Hz), 5.20−5.23 (2H, m), 6.23 (1H, td, J = 6.6, 15.9 Hz), 6.36 (1H, d, J = 15.9 Hz), 6.86−6.88 (2H, m), 7.29−7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 13.7, 17.9, 21.8, 25.5, 35.9, 53.6, 55.3, 56.0, 65.7, 67.2, 114.0, 121.7, 127.0, 130.7, 135.5, 136.2, 142.1, 160.0, 167.2, 195.7; FT-IR (neat) ν 2956, 2931, 2359, 1716, 1699, 1516, 1244, 1101, 1078, 839, 779 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{26}H_{37}O_6Si$ 473.2359, found 473.2385; $[\alpha]^{23}_D$ −14.5 (*c* 0.078, MeOH).

(1*S*,2*S*,6*R*)-2-(*tert*-Butyldimethylsiloxy)-5-oxo-4-pent-1-enyl-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic Acid (**23t**). To a solution of **22t** (32 mg, 0.068 mmol) in CH_2Cl_2 (0.7 mL) was added trifluoroacetic acid (0.07 mL) at room temper-

ature, and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:1−1:3) to afford carboxylic acid **23t** (23 mg, 98%) as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 0.14 (3H, s), 0.21 (3H, s), 0.90 (9H, s), 0.92 (3H, t, J = 7.3 Hz), 1.44 (2H, sextet, J = 7.3 Hz), 1.99−2.21 (2H, m), 3.53 (1H, d, J = 3.9 Hz), 3.72 (1H, dd, J = 3.9 Hz), 5.21 (1H, br-s), 6.32 (1H, td, J = 6.8 Hz, 16.0 Hz), 6.46 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ −4.7, −4.7, 13.7, 17.9, 21.8, 25.5, 36.1, 53.6, 55.7, 65.6, 122.1, 134.5, 137.9, 143.4, 172.6, 196.3; FT-IR (neat) ν 3375, 2929, 2858, 1693, 1680, 1464, 1338, 1099, 781, 741 cm^{-1}; HRMS (FAB) [M + Na]$^+$ calcd for [$C_{18}H_{28}O_5Si$ + Na]$^+$ 375.1604, found 375.1577; [α]$^{22}_D$ −61.4 (*c* 0.11, MeOH).

(2*S*,3*S*,7*R*,8*S*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-8-chlormercurio-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-5,10-dione (**26**). To a solution of carboxylic acid **23t** (21.0 mg, 0.06 mmol) in EtCN (2.1 mL) were added MS4A (6.3 mg, 30 wt %) and $Hg(OTf)_2$/MeCN (0.25 mL, 0.071 mmol) at −78 °C, and the reaction mixture was stirred for 3 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl (1:1). The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:3) to afford **26** (35.0 mg, 99%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.24 (3H, s), 0.87 (9H, s), 0.96 (3H, t, J = 7.3 Hz), 1.49−1.70 (2H, m), 1.77−1.93 (2H, m), 2.82 (1H, br-*d*, J = 11.6 Hz), 3.70 (1H, br-*d*, J = 3.8 Hz), 3.75 (1H, dd, J = 1.9, 3.8 Hz), 4.55 (1H, ddd, J = 3.5, 7.9, 11.6 Hz), 5.43 (1H, br-s); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.9, −4.5, 13.7, 18.2, 25.6, 29.7, 38.8, 42.4, 53.1, 55.4, 61.9, 80.6, 136.5, 142.2, 164.2, 196.9; FT-IR (neat) ν 2958, 2929, 2858, 2360, 1714, 1680, 1252, 1090, 839, 781 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{18}H_{28}ClHgO_5Si$ 589.1101, found 589.1074; [α]$^{23}_D$ +48.8 (*c* 0.087, MeOH).

(2*R*,3*S*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4,7-dien-5,10-dione (**28**). To a solution of carboxylic acid **23t** (100.0 mg, 0.567 mmol) in THF (5.7 mL) was added *p*-benzoquinone (26.2 mg, 2.84 mmol) and $Pd(PhCN)_2Cl_2$ (12.4 mg, 0.0567 mmol) at room temperature, and the reaction mixture was stirred for 20 h. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:3−1:5) to afford **28** (70.0 mg, 70%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (3H, s), 0.26 (3H, s), 0.85 (9H, s), 0.96 (3H, t, J = 7.5 Hz), 1.68 (2H, sextet, J = 7.5 Hz), 2.47 (2H, t, J = 7.5 Hz), 3.63 (1H, br-*d*, J = 3.9 Hz), 3.77 (1H, dd, J = 2.0, 3.9 Hz), 5.29 (1H, br-s), 6.28 (1H, br-s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.6, 13.5, 20.1, 25.7, 35.8, 52.6, 56.7, 61.9, 98.1, 125.4, 139.6, 139.6, 162.3, 166.9, 192.9; FT-IR (neat) ν 2956, 2929, 2856, 1732, 1705, 1641, 1577, 1464, 1257, 1086, 839, 781 cm^{-1}; HRMS (FAB) [M]$^+$ calcd for $C_{18}H_{26}O_5Si$ 350.1550, found 350.1579; [α]$^{23}_D$ −14.1 (*c* 0.17, MeOH).

(2*S*,3*S*,10*R*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-10-hydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4,7-dien-5-one (**29**) **and (2*S*,3*S*,10*S*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-10-hydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4,7-dien-5-one** (**30**). To a solution of **28** (43.0 mg, 0.123 mmol) in MeOH (1.3 mL) was added $NaBH_4$ (14.0 mg, 0.368 mmol) at 0 °C, and the reaction mixture was stirred for 20 min at that temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$) to afford **29** and **30** (42.0 mg, 98%, 50:50 diastereoselectivity) as a colorless oil. **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (3H, s), 0.25 (3H, s), 0.86 (9H, s), 0.96 (3H, t, J = 7.5 Hz), 3.43 (1H, m), 3.52 (1H, m), 4.55 (1H, br-*d*, J = 10.2 Hz), 5.23 (1H, d, J = 2.8 Hz), 5.94 (1H, br-s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.9, 25.7, 29.6, 50.0, 51.3, 62.7, 67.3, 104.7, 117.2, 149.8, 162.5, 166.9; FT-IR (neat) ν 3419, 2927, 2856, 1726, 1651, 1585, 1464, 1254, 1080, 974, 839, 781 cm^{-1}; HRMS (FAB) [M]$^+$ calcd for $C_{18}H_{28}O_5Si$ 352.1706, found 352.1680; [α]$^{23}_D$ +104.1 (*c* 0.08, MeOH). **30**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.22 (3H, s), 0.85 (9H, s), 0.95 (3H, t, J = 7.4 Hz), 1.67 (2H, sextet, J = 7.4 Hz), 2.44 (2H, t, J = 7.4 Hz), 3.47 (1H, dd, J = 2.5, 4.3 Hz), 3.59 (1H, dd, J = 2.2, 4.3 Hz), 4.79 (1H, d, J = 8.8 Hz), 5.12 (1H, d, J = 2.2 Hz), 6.29 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.6, 13.5, 18.1, 20.2, 25.8, 29.7, 35.8, 53.1, 54.4, 62.4, 66.1, 101.4, 117.2, 149.4, 162.3, 165.4; FT-IR (neat) ν 3410, 2929, 2856, 1722, 1645, 1574, 1464, 1252, 1117, 1065, 920, 839, 777 cm^{-1}; HRMS (FAB) [M]$^+$ calcd for $C_{18}H_{28}O_5Si$ 352.1706, found 352.1689; [α]$^{23}_D$ +81.3 (*c* 0.21, MeOH).

(2*S*,3*S*,7*S*,10*R*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-10-hydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-5-one (**31**) **and (2*S*,3*S*,7*R*,10*R*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-10-hydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]-undec-4-en-5-one** (**32**). To a solution of **29** (10.0 mg, 0.0284 mmol) in AcOEt (2.8 mL) was added 10% Pd/C (3.0 mg, 0.0028 mmol) at room temperature, and the reaction mixture was stirred for 3 h under an H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:3) to afford an inseparable mixture of **31** and **32** (9.5 mg, 95%, 95:5 diastereoselectivity) as a colorless oil. **31**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (3H, s), 0.22 (3H, s), 0.85 (9H, s), 0.91 (3H, t, J = 7.3 Hz), 1.37−1.58 (2H, m), 1.74−1.79 (1H, m), 2.29−2.34 (1H, m), 2.38 (1H, dd, J = 4.9, 18.0 Hz), 2.62 (1H, dd, J = 8.4, 18.0 Hz), 3.34−3.36 (1H, m), 3.43−3.45 (1H, m), 4.32 (1H, br-*d*, J = 8.7 Hz), 4.45−4.51 (1H, m), 5.03 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.7, 13.7, 17.9, 18.2, 25.7, 32.0, 36.4, 50.3, 51.8, 62.2, 67.5, 124.3, 148.6, 163.9; FT-IR (neat) ν 3423, 2958, 2931, 2858, 1716, 1254, 1084, 868, 839, 779 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{18}H_{31}O_5Si$ 355.1941, found 355.1948.

(2*S*,3*S*,7*S*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-5,10-dione (**33**). To a solution of **31** and **32** (10.0 mg, 0.0283 mmol) in CH_2Cl_2 (1.0 mL) was added MnO_2 (61.3 mg, 0.705 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:5) to afford **33** (9.2 mg, 92%; 95:5 diastereoselectivity) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (3H, s), 0.45 (3H, s), 0.85 (9H, s), 1.33−1.58 (3H, m), 1.81−1.72 (1H, m), 2.52 (1H, dd, J = 4.6, 18.1 Hz), 2.63 (1H, dd, J = 7.9, 18.1 Hz), 3.56 (1H, br-*d*, J = 3.9 Hz), 3.71 (1H, dd, J = 1.9, 3.9 Hz), 4.48−4.54 (1H,m), 5.16 (1H, br-s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.75, 13.7, 18.1, 18.2, 25.7, 29.7, 36.2, 52.3, 56.4, 61.9, 135.8, 139.5, 163.5, 194.4; FT-IR (neat) ν 2927, 2854, 1726, 1695, 1464, 1252, 1240, 1101, 1084, 839, 781 cm^{-1}; HRMS (FAB) [M + H]$^+$ calcd for $C_{18}H_{29}O_5Si$ 353.1784, found 353.1782; [α]$^{22}_D$ −10.5 (*c* 0.12, MeOH).

(2*R*,3*S*,7*S*,11*R*)-3-Hydroxy-7-propyl-1,6-dioxatricyclo-[8.1.0.0^{4,9}]undec-4-en-5,10-dione (**EI-1941−2** (**2**)). To a solution of **33** (16.6 mg, 0.0471 mmol) in CH_3CN (1.9 mL) was added HF·Pyr (0.5 mL) at 0 °C, and the reaction mixture was stirred for 4 h at that temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:1) to afford EI-1941−2 (**2**) (11.2 mg, quant.) as a colorless powder: ^{1}H NMR (400 MHz, CD_3CN) δ 0.93 (3H, t, J = 7.3 Hz), 1.35−1.51 (2H, m), 1.57−1.66 (1H, m), 1.69−1.78 (1H, m), 2.46 (1H, ddd, J = 1.0 9.7, 18.1 Hz), 2.54 (1H, ddd, J = 1.3, 4.6, 18.1 Hz), 3.56 (1H, dd, J = 1.0, 3.7 Hz), 3.85 (1H, dd,

J = 1.6, 3.7 Hz), 4.46−4.53 (1H, m), 4.97 (1H, br-s); ^{13}C NMR (100 MHz, CD_3CN) δ 12.5, 17.3, 25.3, 35.6, 51.8, 55.8, 60.4, 77.1, 135.1, 140.0, 163.7, 193.9; FT-IR (neat) ν 3448, 2960, 2873, 1716, 1695, 1417, 1244, 1124, 1099, 1041 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{12}H_{15}O_5$ 239.0920, found 239.0932; $[\alpha]^{22}_D$ −299.9 (*c* 0.48, MeOH).

(2*S*,3*S*,7*R*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-8-en-5,10-dione (**37**). To a solution of **26** (5.0 mg, 0.009 mmol) in MeOH (0.1 mL) were added zinc powder (2.8 mg, 0.045 mmol) and AcOH (0.002 mL) at 0 °C, and the reaction mixture was stirred for 10 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was filtered through a pad of Celite, and the organic materials were extracted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:5) to afford **37** (2.7 mg, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (1H, s), 0.12 (1H, s), 0.78 (1H, s), 0.93 (3H, t, J = 7.2 Hz), 1.39−1.53 (2H, m), 1.66−1.76 (2H, m), 3.47 (1H, d, J = 4.1 Hz), 3.52 (1H, q, J = 3.0 Hz), 3.61 (1H, t, J = 4.1 Hz), 5.06 (1H, t, J = 3.0 Hz), 7.05 (1H, t, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.1, −4.8, 14.0, 18.2, 25.9, 38.8, 40.7, 54.8, 56.6, 67.5, 79.5, 127.9, 135.1, 168.3, 190.7; FT-IR (neat) ν 2927, 2856, 1743, 1709, 1655, 1464, 1389, 1117, 839, 781 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{18}H_{29}O_5Si$ 353.1784, found 353.1791; $[\alpha]^{23}_D$ −31.6 (*c* 0.113, MeOH).

(2*R*,3*S*,7*R*,11*R*)-3-Hydroxy-7-propyl-1,6-dioxatricyclo-[8.1.0.0^{4,9}]undec-8-en-5,10-dione (**38**). To a solution of **37** (3.5 mg, 0.01 mmol) in CH_3CN (0.2 mL) was added HF·Pyr (0.05 mL) at room temperature, and the reaction mixture was stirred for 6 h at that temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:1) to afford **38** (2.4 mg, quant.) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.4 Hz), 1.38−1.60 (2H, m), 1.67−1.79 (2H, m), 3.52−3.55 (2H, m), 3.79 (1H, dd, J = 3.8, 3.6 Hz), 5.14 (1H, dd, J = 3.1, 3.6 Hz), 7.13 (1H, t, J = 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.1, 37.0, 41.1, 54.0, 55.3, 65.0, 79.6, 127.3, 135.9, 169.0, 189.7; FT-IR (neat) ν 2956, 2927, 2854, 1743, 1709, 1655, 1250, 1117, 1061, 839, 781 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{12}H_{15}O_5$ 239.0920, found 239.0909; $[\alpha]^{32}_D$ +37.4(*c* 0.113, MeOH).

(2*R*,3*S*,7*R*,11*R*)-3,5-Dihydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-10-one (**epi-EI-1941−2** (**39**)). To a solution of **38** (5.8 mg, 0.024 mmol) in CH_2Cl_2 (0.24 mL) was added Et_3N (1.7 μL, 0.012 mmol) at room temperature, and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with buffer, and diluted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:1) to afford epi-EI-1941−2 (**39**) (3.5 mg, 67%) as a colorless powder: ^{1}H NMR (400 MHz, CD_3CN) δ 0.95 (3H, t, J = 7.3 Hz), 1.55−1.38 (2H, m), 1.77−1.62 (2H, m), 2.88 (1H, dd, J = 3.4, 18.1 Hz), 3.59 (1H, dd, J = 1.0, 3.6 Hz), 3.84 (1H, dd, J = 1.5, 3.6 Hz), 4.35−4.42 (1H, m), 5.11 (1H, br-s); ^{13}C NMR (100 MHz, CD_3CN) δ 14.1, 18.7, 26.3, 36.3, 53.3, 57.0, 61.3, 78.7, 136.5, 141.3, 165.5, 194.4; FT-IR (neat) ν 3438, 2958, 2871, 1716, 1697, 1417, 1124, 1113, 1246, 1041 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{12}H_{15}O_5$ 239.0920, found 239.0922; $[\alpha]^{23}_D$ −29.5 (*c* 0.087, MeOH).

(2*R*,3*R*,7*R*,10*S*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-5,10-diol (**40**). To a solution of **31** and **32** (9.0 mg, 0.0254 mmol) in CH_2Cl_2 (0.9 mL) was added a hexane solution of DIBAL-H (0.94 M, 0.09 mL, 0.0787 mmol) at −90 °C under an argon atmosphere, and the reaction mixture was stirred for 20 min at that temperature. The reaction mixture was quenched with saturated aqueous Rochelle salt. The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:3) to afford **40** (6.9 mg, 80%, 95:5 diastereoselectivity) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (3H, s), 0.17 (3H, s), 0.89 (9H, s), 0.91 (3H, t, J = 7.2 Hz), 1.32−1.60 (2H, m), 1.80 (1H, dd, J = 1.9, 15.5 Hz), 1.88 (1H, br-*d*, J = 11.1 Hz), 2.32 (1H, dd, J = 11.1, 17.4 Hz), 2.62 (1H, br-*d*, J = 5.3 Hz), 3.23−3.24 (1H, m), 3.38−3.39 (1H, m), 3.93 (1H, ddt, J = 4.3, 7.5, 11.1 Hz), 4.18 (1H, br-*d*, J = 9.9 Hz), 4.59 (1H, br-s), 5.37 (1H, d, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.5, 14.0, 18.0, 18.5, 25.8, 33.3, 37.2, 52.5, 52.7, 63.3, 65.8, 67.4, 88.8, 129.1, 131.6; FT-IR (neat) ν 3410, 2956, 2929, 2858, 2364, 2341, 1259, 1082, 1059, 1003, 974, 837, 779 cm^{-1}; HRMS (FAB) $[M]^+$ calcd for $C_{18}H_{32}O_5Si$ 356.2019, found 356.2004; $[\alpha]^{22}_D$ −7.13 (*c* 0.70, MeOH).

(2*R*,3*R*,7*R*,11*S*)-3-(*tert*-Butyldimethylsiloxy)-5-hydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-10-one (**42**). To a solution of **40** (10.5 mg, 0.0295 mmol) in CH_2Cl_2 (1.0 mL) was added MnO_2 (64.0 mg, 0.736 mmol) at 0 °C under an argon atmosphere, and the reaction mixture was stirred for 1 h at that temperature. The reaction mixture was filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:5) to afford **42** (10.0 mg, 95%; 95:5 diastereoselectivity) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (3H, s), 0.19 (3H, s), 0.89 (9H, s), 0.91 (3H, t, J = 7.3 Hz), 1.38−1.61 (2H, m), 2.06 (1H, dd, J = 10.8, 17.6 Hz), 2.18 (1H, br-*d*, J = 17.6 Hz), 2.80 (1H, br-s), 3.47 (1H, dd, J = 1.0, 3.6 Hz), 3.61 (1H, dd, J = 1.0, 3.6 Hz), 3.86−3.92 (1H, m), 4.82 (1H, br-s), 5.56 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.3, 13.9, 18.0, 18.4, 25.6, 27.7, 37.1, 52.6, 57.6, 63.3, 66.3, 88.0, 129.8, 146.0, 193.4; FT-IR (neat) ν 3431, 2956, 2931, 2860, 1684, 1464, 1259, 1074, 866, 739 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{18}H_{32}O_5Si$ 356.2019, found 356.1990; $[\alpha]^{21}_D$ −137.2 (*c* 0.593, MeOH).

(2*R*,3*R*,7*R*,11*S*)-3,5-Dihydroxy-7-propyl-1,6-dioxatricyclo[8.1.0.0^{4,9}]undec-4-en-10-one (EI-1941−1 (**1**)). To a solution of **42** (6.0 mg, 0.0169 mmol) in CH_3CN (0.5 mL) was added HF·Pyr (0.05 mL) at room temperature, and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with AcOEt, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:1) to afford EI-1941−1 (**1**) (3.2 mg, 94% based on conversion) as a brownish oil: ^{1}H NMR (400 MHz, CD_3CN) δ 0.92 (1H, t, J = 7.2 Hz), 1.35−1.54 (4H, m), 1.96 (1H, br-dd, J = 11.1, 17.7 Hz), 2.09 (1H, ddd, J = 1.8, 3.2, 17.7 Hz), 3.43 (1H, dd, J = 1.0, 3.7 Hz), 3.74 (1H, dd, J = 1.3, 3.7 Hz), 3.85 (1H, m), 4.59 (1H, br-s), 5.51 (1H, s); ^{13}C NMR (100 MHz, CD_3CN) δ 14.2, 19.2, 28.3, 37.9, 53.4, 57.7, 62.9, 66.3, 88.2, 129.9, 148.3, 194.9; FT-IR (neat) ν 3419, 2960, 2933, 2873, 1682, 1456, 1281, 1028, 874, 725 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{12}H_{17}O_5$ 241.1076, found 241.1075; $[\alpha]^{20}_D$ −188.8 (*c* 0.16, MeOH).

(3*R*,7*R*,8*R*)-7,8-Dihydroxy-3-propylisochromene-1,5-dione (EI-1941−3 (3)). To a solution of EI-1941−2 (**2**) (4.6 mg, 0.0193 mmol) in THF (0.39 mL) was added a THF solution of SmI_2 (0.1 M, 0.58 mL, 3.0 mmol) at −90 ° C under an argon atmosphere, and the reaction mixture was stirred for 20 min at that temperature. The reaction mixture was quenched with pH 7.0 phosphate buffer, and diluted with AcOEt. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:0) to afford EI-1941−3 (**3**) (4.5 mg, 98%) as a reddish oil: ^{1}H NMR (400 MHz, CD_3CN) δ 0.94 (3H, t, J = 7.3 Hz), 1.35−1.56 (1H, m), 1.60−1.69 (1H,

m), 1.71−1.80 (1H, m), 2.26 (1H, br-dd, J = 11.3, 18.2 Hz), 2.51 (1H, dd, J = 4.0, 16.7 Hz), 2.76 (1H, ddd, J = 1.4, 3.9, 18.2 Hz), 2.93 (1H, dd, J = 3.0, 16.7 Hz), 3.38 (1H, br-s), 3.76 (1H, br-s), 4.22 (1H, q, J = 3.2 Hz), 4.42−4.49 (1H, m); ^{13}C NMR (100 MHz, CD_3CN) δ 14.1, 18.9, 26.3, 37.4, 41.7, 66.7, 70.5, 79.0, 136.9, 143.6, 167.0, 197.7; FT-IR (neat) ν 3419, 2960, 2933, 2873, 1716, 1693, 1410, 1230, 1024 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $C_{12}H_{17}O_5$ 241.1076, found 241.1076; $[\alpha]^{30}_D$ −88.7 (*c* 0.28, MeOH).

(1*S*,2*S*,6*R*)-2-Hydroxy-5-oxo-4-pent-1-enyl-7-oxabicyclo-[4.1.0]hept-3-ene-3-carboxylic Acid (45). To a solution of **23t** (5.0 mg, 0.014 mmol) in MeOH (0.05 mL) was added Dowex 50W-X4 (10.0 mg), and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (MeOH/$CHCl_3$ = 1:10) to afford carboxylic acid **45** (2.3 mg, 93%) as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 0.92 (3H, t, J = 7.3 Hz), 1.45 (2H, sextet, J = 7.3 Hz), 2.11 (2H, q, J = 6.9 Hz), 3.54 (1H, d, J = 3.9 Hz), 3.77 (1H, d, J = 3.9 Hz), 5.00 (1H, br-s), 6.33 (1H, dt, J = 6.9, 16.1 Hz), 6.45 (1H, d, J = 16.1 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 13.9, 23.1, 36.9, 55.0, 57.3, 65.9, 123.5, 134.1, 141.3, 143.0, 174.6, 197.2; FT-IR (neat) ν 3342, 2960, 2925, 2873, 2854, 2360, 1695, 1633, 1576, 1261, 1041, 970, 739 cm^{-1}; HRMS (FAB) $[M + H]^+$ calcd for $[C_{12}H_{14}O_5 + H]^+$ 239.0919, found 239.0934; $[\alpha]^{25}_D$ −73.8 (*c* 0.32, MeOH).

(2*R*,3*S*,11*S*)-3-Hydroxy-7-propyl-1,6-dioxatricyclo-[8.1.0.0^{4,9}]undec-4,7-dien-5,10-dione (46). To a solution of **28** (3.6 mg, 0.0074 mmol) in MeOH (0.05 mL) was added Dowex 50W-X4 (7.2 mg), and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (AcOEt/hexane = 1:5) to afford **46** (1.7 mg, 97%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz), 1.67 (2H, sextet, J = 7.5 Hz), 2.50 (2H, t, J = 7.5 Hz), 3.66 (1H, d, J = 3.5 Hz), 3.94 (1H, dd, J = 1.4, 3.5 Hz), 5.28 (1H, br-s), 6.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 20.2, 35.8, 52.8, 56.6, 61.4, 98.2, 125.7, 139.1, 163.4, 166.9, 191.4; FT-IR (neat) ν 3431, 2964, 2931, 2875, 1722, 1705, 1641, 1577, 1045, 852, 760 cm^{-1}; HRMS (FAB) $[M]^+$ calcd for $C_{12}H_{12}O_5$ 236.0685, found 236.0664; $[\alpha]^{24}_D$ −96.1 (*c* 0.43, MeOH).

Measurement of Interleukin-1*β*) Secretion. THP-1 cells were suspended in RPMI1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum, and seeded on 48-well plates (5×10^4 cells/well). The cells were differentiated with 30 nM of pharbol-12-myristate-13-axetate (PMA) for 72 h. After the plate was rinsed with serum-free RPMI1640 medium to remove unadherent cells, adherent cells were stimulated with 100 μg/ml of lipopolysaccharide (LPS; Sigma) for 4 h in the presence of various concentrations of test compounds. The culture media were harvested, and mature IL-1β was measured by an ELISA method using an IL-1β assay kit (Amersham Biosciences, Tokyo, Japan).

Measurement of Cell Viability. THP-1 cells (2.5×10^4 cells/well) were differentiated with 30 nM PMA as described above. The differentiated cells were then treated with test compounds for 4 h. The cell number was evaluated by the subsequent color reaction. WST-8 solution 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium, monosodium salt (Nacalai tesque, Kyoto, Japan), was added to the medium, and the cells were further incubated for 3 h at 37 °C. The absorbance (A_{450}) of each well was measured using a plate reader (Wallac 1420 multilabel counter; Amersham Biosciences). Cell viability (%) was calculated as (experimental absorbance − background absorbance)/(control absorbance − background absorbance) × 100.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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