De Novo Synthesis of Possible Candidates for the Inagami-Tamura Endogenous Digitalis-Like Factor (EDLF)

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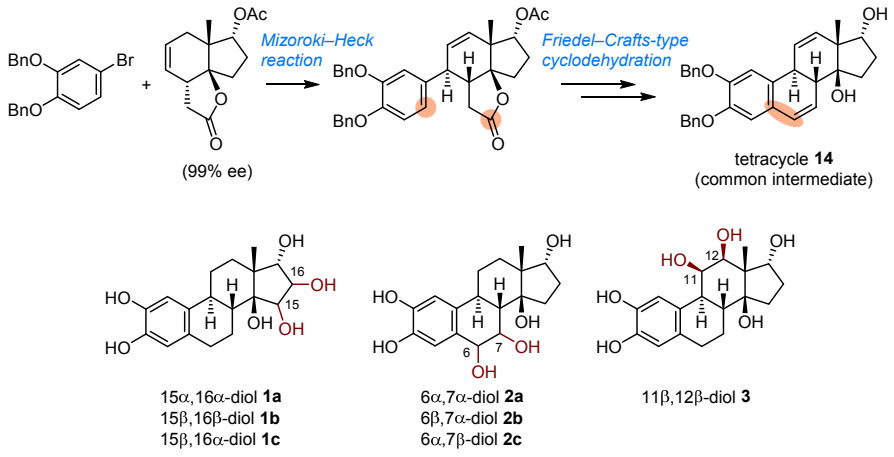
ABSTRACT: The *de novo* synthesis of possible candidates for the Inagami-Tamura endogenous digitalis-like factor (EDLF) was achieved in order to validate a previously proposed structure. Our synthetic approach involves a highly regio- and diastereoselective Mizoroki–Heck reaction and a Friedel–Crafts-type cyclodehydration to construct steroidal tetracycle **14** as a versatile common intermediate leading to seven 2,14β-dihydroxyestradiol analogues **1a-c**, **2a-c**, and **3** as possible candidates. By comparing the potency of inhibitory activity against Na^+/K^+-ATPase between the synthesized candidates and the EDLF, it was found that the proposed structure is not likely to be a true structure of the Inagami-Tamura EDLF.



INTRODUCTION

Cardiotonic steroids are originally isolated from plants, toads, snakes, and insects,[1] and they cause an increase in calcium concentration through the inhibition of Na^+/K^+-ATPase, leading to contraction of cells.[2] Cardiotonic steroids possess common structural features: (1) a β-hydroxy group at C14 in a steroidal scaffold bearing *cis*-fused AB and CD rings, (2) a β-configured 5- or 6-membered unsaturated lactone moiety at C17 (cardenolides or bufadienolides, respectively), and (3) the presence of a variable number of sugar residues at C3. Lactones are considered to be the most essential functional group for biological activity of these molecules.[3] A variety of the related steroids has also been isolated from mammalian tissues and fluids. These still unidentified compounds are referred to as the endogenous digitalis-like factor (EDLF) (Figure 1).[4] Ouabain, the most well-known EDLF candidate, has been isolated from human plasma[5a] and bovine hypothalamus[5b] and structurally characterized by FABMS and ^{1}H NMR. Although EDLF plays a role in various disorders, most EDLF structures remain ambiguous because the obtained amounts are typically quite small.

A candidate for EDLF was isolated from bovine adrenal by Inagami and Tamura in 1987.[6] This compound, named Inagami-Tamura EDLF, exhibited all of the representative properties of an EDLF: (1) potent inhibitory activity against Na^+/K^+-ATPase (postulated IC_{50}: 9.9 ~ 182 nM) comparable to ouabain (IC_{50}: 23 nM); (2) competitive displacement activity against [^{3}H]-ouabain bound to the enzyme; (3) inhibitory activity for ^{86}Rb uptake into intact human erythrocytes; and (4) cross-reactivity with anti-digoxin-specific antibody. Overall, this compound functioned in a manner similar to that of ouabain. FAB-LRMS spectra showed an *m*/*z* value of 336, and biological evaluation suggested that it possesses a steroidal scaffold

rather than a lipid or peptide composition. NMR spectra could not be acquired due to the insufficient amount isolated (multi-micrograms), and therefore, the structure has not been elucidated.

In 1996, Sakakibara and Uchida proposed a 2,14β-dihydroxyestradiol analogue having two hydroxy groups, compound **A**, as a structural candidate for the Inagami-Tamura EDLF based on this limited information and their own deductions (Figure 2).[7] Compound **A** possesses a unique structural motif not found in other reported EDLF candidates such as ouabain, owing to its unsaturated A-ring moiety. Sakakibara and Uchida envisaged that the positions and stereochemistries of the residual hydroxy groups on the dihydroxyestradiol basic scaffold could be determined by comparison of the inhibitory activity of synthetic compounds. However, two possible candidates semi-synthesized from estradiol, **1a** and **1b**, exhibited low contractile activity of isolated rat aorta and guinea pig left atrium, indicating insufficient potency for the Inagami-Tamura EDLF.[7] The validity of the basic scaffold, as well as the positions and the stereochemistries of two hydroxy groups, have not been explored further. In order to validate the structure proposed by Sakakibara, we embarked on the synthesis of proposed 2,14β-dihydroxyestradiol analogues and an evaluation of their biological activities. In this report, we describe the *de novo* synthesis[8] of seven possible candidates and their inhibitory activity of Na^+/K^+-ATPase. Our synthetic approach involves a highly regio- and diastereoselective Mizoroki–Heck reaction and a Friedel–Crafts-type cyclodehydration to construct a steroidal tetracycle as a common intermediate. This steroidal intermediate allows facile construction of the proposed 2,14β-dihydroxyestradiol analogues such as **1a-c**, **2a-c**, and **3** (Figure 2) since this intermediate possesses an alkene on the B- and C-rings for the introduction of hydroxy

groups. Furthermore, our *de novo* approach offers a new and facile entry to a variety of other estradiol analogues with different functionalities.[9]

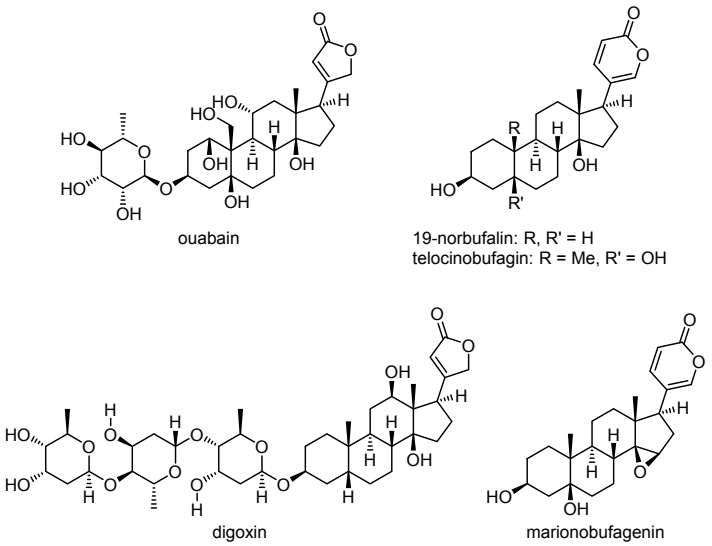


Figure 1. Structures of the reported EDLF candidates.

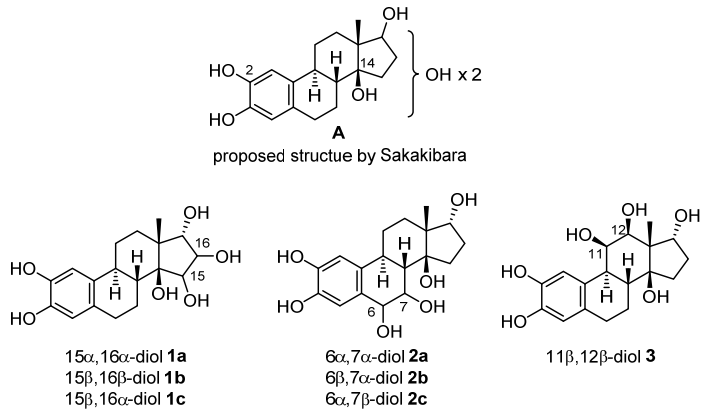
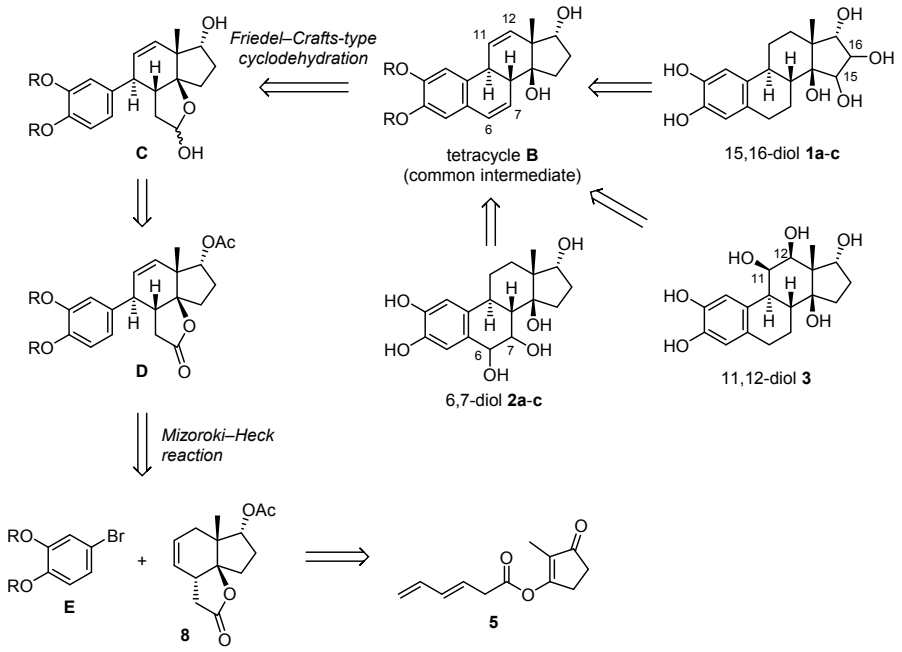


Figure 2. Proposed structure **A** of the Inagami-Tamura EDLF and its possible candidates **1a-c**, **2a-c** and **3**.

SYNTHETIC PLAN

Our synthetic plan is depicted in Scheme 1. In contrast to Sakakibara's semi-synthesis of **1a** and **1b** from estradiol,[7] we decided to adopt the *de novo* synthesis of the possible candidates **1a-c**, **2a-c** and **3** from a steroidal tetracycle like **B** as a common intermediate in order to introduce hydroxy groups into the B- and C-rings. Tetracycle **B** would be synthesized by the Friedel–Crafts-type cyclodehydration of lactol **C**. An aryl group in lactone **D**, a precursor of lactol **C**, would be stereoselectively introduced by means of the Mizoroki–Heck reaction of lactone **8** with bromoarene **E** from the convex face of the tricyclic lactone system. Tricyclic lactone **8** bearing a *cis*-hydroindane scaffold would in turn be furnished by a newly designed intramolecular Diels–Alder reaction of enol ester **5** and subsequent optical resolution.

Scheme 1. Synthetic plan for candidates **1a-c**, **2a-c**, and **3**.



RESULTS AND DISCUSSION

Synthesis of lactone 8. In order to obtain enantioenriched tricyclic lactone **8** at the outset, we synthesized enol ester **5**, a substrate of intramolecular Diels–Alder reaction, from commercially available ethyl sorbate (Scheme 2). Thus, isomerization of ethyl sorbate was carried out under conventional conditions to obtain β,γ-unsaturated ester **4a**, which was then hydrolyzed to afford corresponding carboxylic acid **4b**. Transformation of **4b** into an acid chloride and subsequent treatment with 2-methyl-1,3-cyclopentanedione in the presence of Et_3N afforded enol ester **5** in good overall yield. Intramolecular Diels–Alder reaction of **5** was conducted at 200 °C with BHT in 1,2,4-trichlorobenzene to provide the desired *endo*-**6** in 66% as a major diastereomer along with *exo*-**6** in 19% yield.[10] A decagram-scale synthesis of *endo*-**6** could be performed from carboxylic acid **4b** (34% in 3 steps). The ketone carbonyl group in *endo*-**6** was then reduced with $NaBH_4$ in MeOH to afford alcohol (±)-**7** in 82% yield. The relative stereochemistry of *endo*-**6** and (±)-**7** was determined by NOESY analysis as shown in Figure 3, which revealed that the reduction took place preferentially from the convex face of the scaffold. With racemic alcohol (±)-**7** in hand, optical resolution was next conducted. After several attempts at kinetic resolution with various enzymes, it was found that the resolution with lipase MY-30 (Meito Sangyo Co. Ltd., Japan) in the presence of vinyl acetate and subsequent recrystallization afforded the enantiomerically pure acetate **8** and alcohol **7** in good yield on a multigram scale. The absolute configuration of **8** was unambiguously established by single-crystal X-ray diffraction analysis by using the Bijvoet method.[11]

Scheme 2. Synthesis of enantioenriched acetate **8** and alcohol **7**.

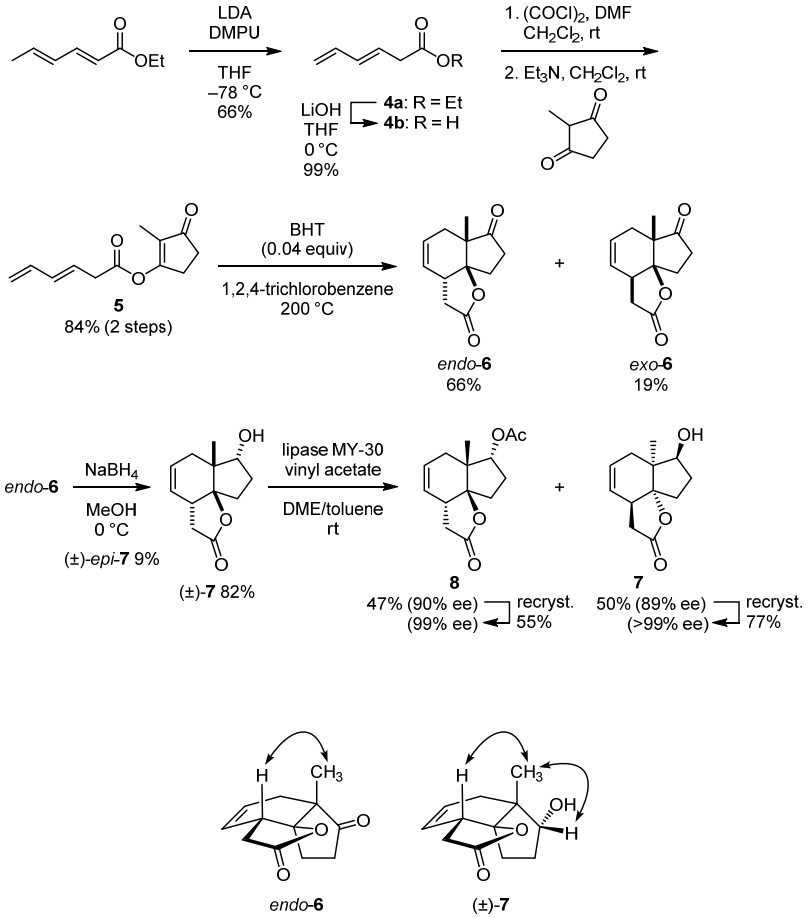


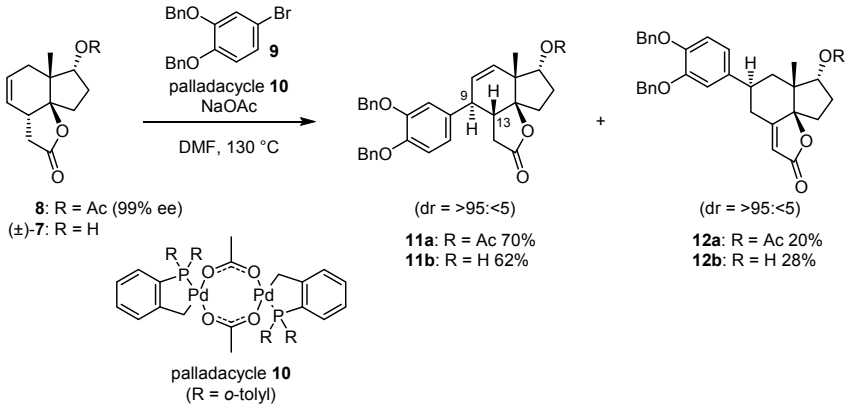
Figure 3. Diagnostic NOESY correlations of *endo*-**6** and alcohol (±)-**7**.

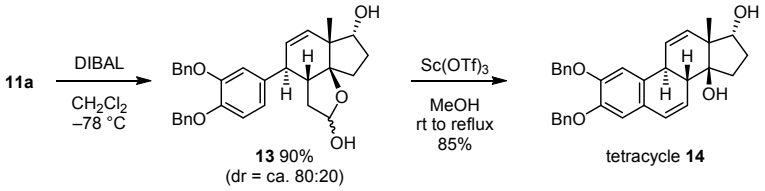
Synthesis of tetracycle 14, a common intermediate. We next investigated a Mizoroki–Heck reaction using acetate **8** (Scheme 3). The Mizoroki–Heck reaction of acetate **8** and bromoarene **9**[12] with palladacycle **10** as a catalyst, reported by Herrmann and co-workers,[13] resulted in the formation of the desired product **11a** in 70% yield along with its regioisomer **12a** in 20% yield. Both compounds were obtained as a single diastereomer. Alcohol (±)-**7** also underwent the related transformation with **9** to afford **11b** and **12b** in 62% and 28% yields, respectively. The observed regioselectivity could be attributed to steric hindrance by the buttressing effect of the

angular methyl group. The relative stereochemistry of alcohols **11b** and **12b** was confirmed by NOESY correlations, as shown in Figure 4. The relative stereochemistry of acetates **11a** and **12a** was confirmed by derivatizations from **11b** and **12b**, respectively. The stereochemical outcomes indicate that the Mizoroki–Heck reactions took place from the convex face of the tricycic lactone system, as anticipated. Thus, the present Mizoroki–Heck reaction enables stereoselective installation of the A-ring fragment into **11a** with a proper C9-stereochemistry for construction of a *trans*-BC ring junction in a steroidal tetracyclic system **14**.[14]

The second key reaction leading to the steroid scaffold was next examined. Aryl adduct **11a** was converted into lactol **13** by DIBAL reduction, and subsequent Friedel–Crafts-type cyclodehydration of **13** provided tetracycle **14**, a common and indispensable intermediate, in good yield. A combination of $Sc(OTf)_3$/MeOH was crucial for this transformation;[15] other systems such as $Sc(OTf)_3/CH_2Cl_2$, *p*-TsOH/$(CH_2Cl)_2$, TFA/$(CH_2Cl)_2$, and $BF_3{\cdot}OEt_2/CH_2Cl_2$ only furnished a complex mixture instead of the desired **14**.

Scheme 3. Synthesis of tetracycle **14** through Mizoroki–Heck reaction and Friedel–Crafts-type cyclodehydration.





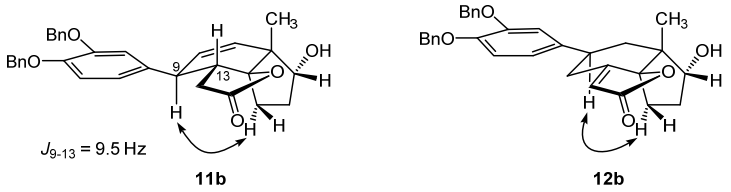


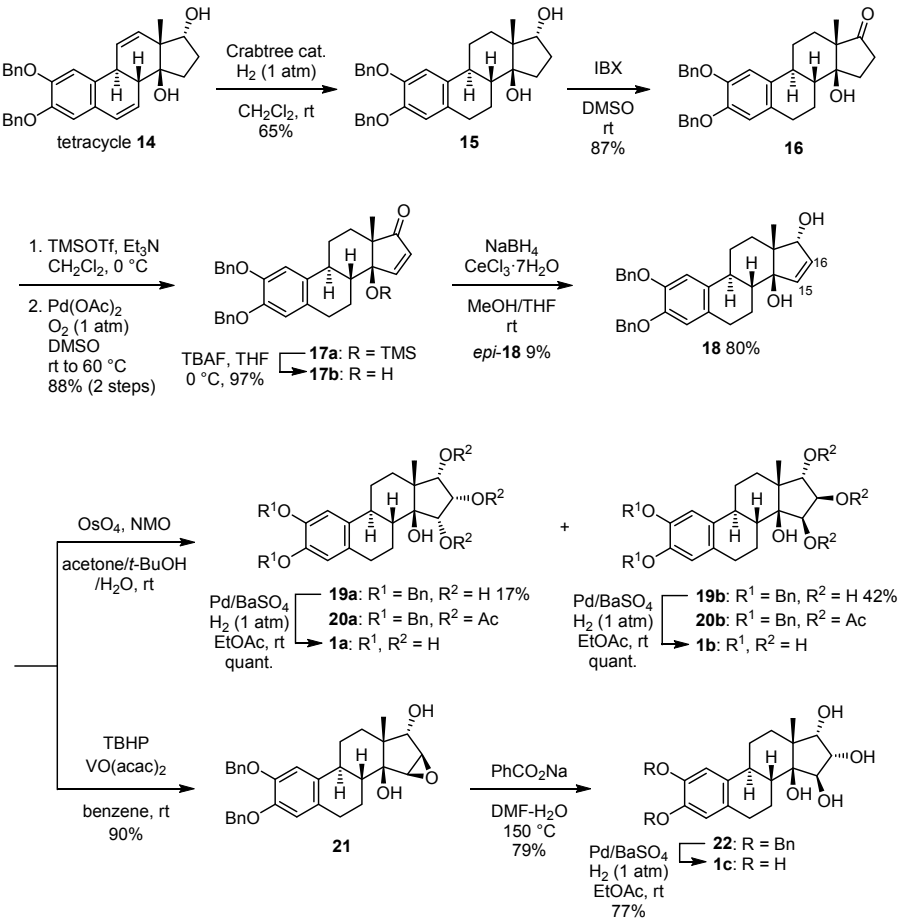
Figure 4. Diagnostic NOESY correlations of **11b** and **12b**.

Synthesis of possible candidates 1a-c from tetracycle 14. With key steroidal intermediate **14** in hand, we moved on to the synthesis of possible candidates **1a-c** for the Inagami-Tamura EDLF, as depicted in Scheme 4. Hydrogenation of the C=C bonds in tetracycle **14** with the Crabtree's catalyst under a hydrogen atmosphere (1 atm) provided **15** in 65% yield. Oxidation of the secondary alcohol in **15** led to ketone **16** which was treated with TMSOTf and Et_3N to provide the silyl enol ether with a

TMS-protected tertiary hydroxy group. Subsequent Ito-Saegusa reaction[16] of the resulting silyl enol ether led to enone **17a** in 88% yield (2 steps). After deprotection of the TMS group, treatment of the resulting enone **17b** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in MeOH at rt afforded **18** in 80% yield and *epi*-**18** in 9% yield. Dihydroxylation of the resulting allylic alcohol **18** using OsO_4/NMO provided known compounds **19a** and **19b** as a separable mixture in 17% and 42% yields, respectively. It is worth noting that diols **19a** and **19b** were directly separated by using Chromatorex®-DIOL (Fuji Silysia Chemical Ltd., Japan), whereas in the previous report[7] they were separated after derivatization into the corresponding acetates. Finally, deprotection of the benzyl groups in **19a** and **19b** was successfully carried out with Pd/$BaSO_4$ under a hydrogen atmosphere (1 atm) to afford the corresponding **1a** and **1b**, respectively.[7] The ^1H and ^{13}C NMR spectra of synthesized compounds **19a**, **19b**, **1a** and **1b** were in agreement with those reported; however, subtle differences in chemical shifts were observed. Therefore, we identified **19a** and **19b** after acetylation to triacetates **20a** and **20b**. The ^1H and ^{13}C NMR spectra of **20a** and **20b** were identical to those previously reported.

In order to obtain 15,16-*trans*-diol **1c**, epoxidation of allylic alcohol **18** under the Sharpless conditions [$VO(acac)_2$, TBHP][17] was followed by ring-opening of the resulting epoxide **21** by using $PhCO_2Na$ at 150 °C to provide *trans*-diol **22**.[18] Finally, deprotection of the benzyl groups by the same manner afforded the corresponding **1c** in good overall yields. The newly generated stereogenic centers of **22** were determined by NOESY correlation between the C9 and C15 protons, as shown in Figure 5.

Scheme 4. Synthesis of 15,16-diols **1a** and **1b** and 15,16-*trans*-diol **1c** from tetracycle **14**.



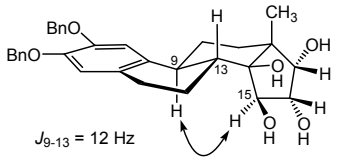
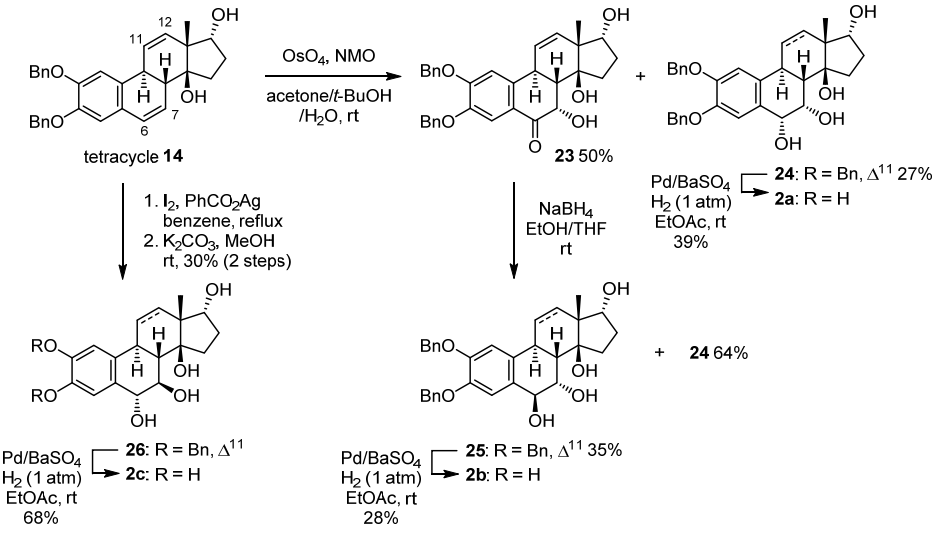


Figure 5. Diagnostic NOESY correlations of 15,16-diol **22**.

Synthesis of possible candidates 2a-c from tetracycle 14. Tetracycle **14** was then converted into 6,7-diols **2a-c** (Scheme 5). The buttressing effect of the angular

methyl group in **14** was expected to allow discrimination of the two alkenes at the C6-C7 and C11-C12. Indeed, oxidation of **14** with OsO_4 and NMO afforded desired 6,7-*cis*-diol **24** in 27% yield as a minor product and hydroxy ketone **23** in 50% yield. Hydroxy ketone **23** was not an expected product but a useful intermediate to obtain 6,7-*trans*-diol **25**. Reduction of **23** with $NaBH_4$ afforded a separable mixture of 6,7-*trans*-diol **25** and 6,7-*cis*-diol **24**. Deprotection of the benzyl groups and hydrogenation of the remaining C11-C12 alkene in the resulting **24** and **25** were performed under the same conditions [$Pd/BaSO_4$, H_2 (1 atm), EtOAc] leading to the candidates **2a** and **2b**, respectively. On the other hand, Prevost reaction of tetracycle **14** provided the corresponding dibenzoate, which was then hydrolyzed to afford the other 6,7-*trans*-diol **26**. Final deprotection and hydrogenation also succeeded to obtain **2c** in the same manner. The relative stereochemistry of **24** and **26** were determined by NOESY analysis (Figure 6).

Scheme 5. Synthesis of 6,7-diol **2a-c** from common intermediate **14**.



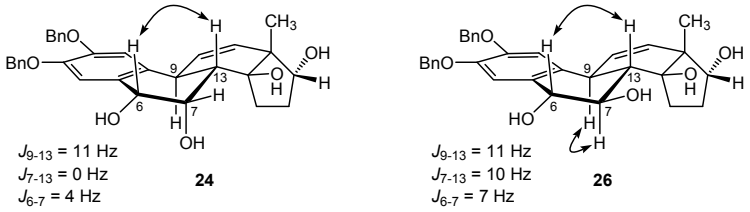
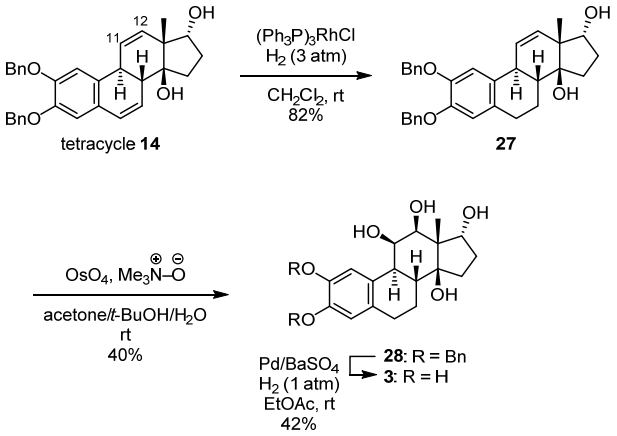


Figure 6. Diagnostic NOESY correlations of **24** and **26**.

Synthesis of possible candidate 3 from tetracycle 14. Final candidate **3** was synthesized from tetracycle **14** (Scheme 6). Regioselective hydrogenation of the sterically less congested alkene in **14** was carried out with Wilkinson's catalyst in 82% yield. Subsequent dihydroxylation with trimethylamine *N*-oxide[19] resulted in the exclusive formation of β-*cis*-diol **28** in moderate yield. The relative stereochemistry of **28** was determined by NOESY analysis, as depicted in Figure 7. Final deprotection of the benzyl groups in **28** furnished 11,12-*cis*-diol **3** in 42% yield.

Scheme 6. Synthesis of 11,12-diol **3** from common intermediate **14**.



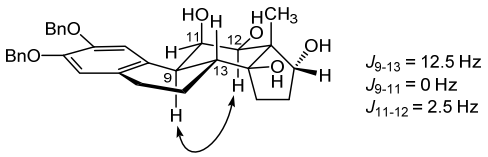


Figure 7. Diagnostic NOESY correlations of 11,12-diol **28**.

EVALUATION OF INHIBITORY ACTIVITY

We investigated the inhibitory activity of seven synthesized analogues **1a-c**, **2a-c**, and **3** against Na^+/K^+-ATPase from porcine cerebral cortex by colorimetric phosphate quantitation using malachite green (Figure 8). Ouabain (OUA) was used as a positive control. The inhibitory activities of the seven compounds were lower than that of OUA at a final concentration of 3 μM (Figure 7, a). At a final concentration of 300 μM, some of the synthesized compounds such as **1a-c** and **3** showed inhibitory activities comparable to that of ouabain at 3 μM (Figure 7, b). In this study, the synthesis and evaluation of the inhibitory activities were not examined for all possible dihydroxylated regio- and stereoisomeric analogues. However, based on the general trend observed here for the structure and activity, other 2,14β-dihydroxyestradiol analogues seem to exhibit less potent inhibitory activities than that of OUA as well, even by changing position and stereochemistry of the hydroxy groups. From the view point of the potent inhibitory activity reported by Inagami and Tamura,[6] the structure proposed by Sakakibara is not likely to be a true structure of the Inagami-Tamura EDLF and the basic scaffold may be incorrect.

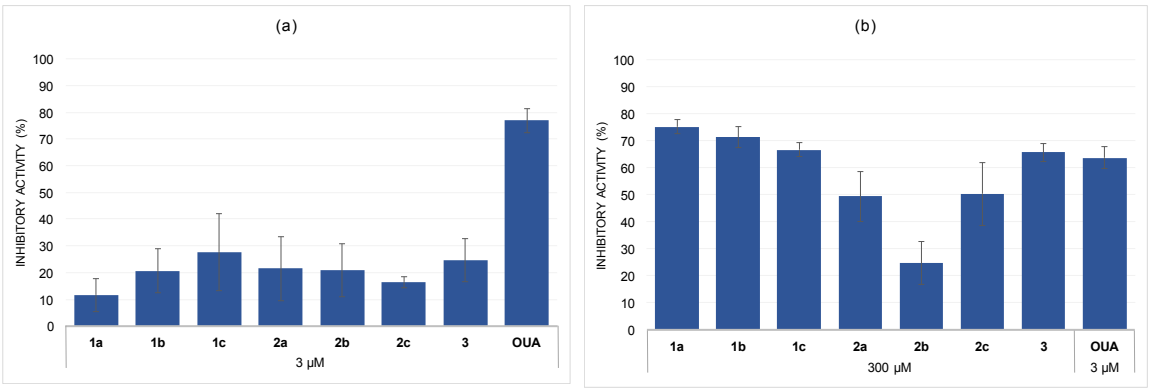


Figure 8. Inhibitory activity of synthesized compounds **1a-c**, **2a-c**, and **3**. (a) At a final concentration of 3 μM. (b) At a final concentration of 300 μM for synthesized compounds and 3 μM for OUA (ouabain). The results shown are the means of three independent experiments ± S.D (*error bars*).

CONCLUSION

We have developed the *de novo* synthesis of seven dihydroxylated 2,14β-dihydroxyestradiol analogues to validate Sakakibara's proposed structure for the Inagami-Tamura EDLF. A newly designed intramolecular Diels–Alder reaction of enol ester **5** enables construction of functionalized tricyclic lactone *endo*-**6** on a decagram scale. Optical resolution of alcohol (±)-**7** with lipase MY-30 and subsequent recrystallization provided enantiomerically pure acetate **8** in good yield. Two key transformations, a highly regio- and stereoselective Mizoroki–Heck reaction using Herrmann palladacycle **10** and a Friedel–Crafts-type cyclodehydration with $Sc(OTf)_3$/MeOH, allowed for synthesis of steroidal tetracycle **14** in good overall yield. Finally, tetracycle **14**, a versatile intermediate, was successfully converted into seven 2,14β-dihydroxyestradiol analogues **1a-c**, **2a-c**, and **3**. We are hopeful that this newly developed *de novo* approach will provide a facile entry to a wide variety of other

estradiol analogues with functionalities on the B- and C-rings, which are otherwise difficult to obtain.[9] As all of these synthetic analogues of Sakakibara's proposed structure exhibited low inhibitory activity against Na^+/K^+-ATPase, basic scaffold of the proposed structure may be incorrect. It is reasonable to expect that further confirmation of the structure for the Inagami-Tamura EDLF would eventually be achieved through reisolation and characterization based on NMR studies of the compound.

EXPERIMENTAL SECTION

General Techniques. Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 type A spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian Gemini-2000 (300 MHz), a Bruker Avance-400 (400 MHz), or a Bruker ARX-400 (400 MHz) spectrometer. Chemical shifts of all compounds are reported in ppm relative to the residual undeuterated solvent ($CDCl_3$ as $\delta = 7.26$, CD_3OD as $\delta = 3.31$, DMSO-d_6 as $\delta = 2.50$, acetone-d_6 as $\delta = 2.05$). Data were reported as follows: Chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened), coupling constant(s), and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini-2000 (75 MHz), a Bruker Avance-400 (100 MHz), a Bruker ARX-400 (100 MHz) or a Bruker Avance-600 (150 MHz) spectrometer. Chemical shifts of all compounds are reported in ppm relative to the solvent ($CDCl_3$ as $\delta = 77.0$, CD_3OD as $\delta = 49.0$, DMSO-d_6 as $\delta = 39.5$, acetone-d_6 as $\delta = 29.8$). All NMR were measured at 300 K. High-resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner ESI-TOF spectrometer for ESI-MS, and reported in m/z. Elemental analyses were performed by the Analytical Laboratory of Graduate School of Bioagricultural Sciences, Nagoya University. Melting points (mp) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Absorbance was measured on a SPECTRAmax 250 microplate spectrophotometer.

All reactions were monitored by thin layer chromatography (TLC) on 0.25 mm silica gel coated glass plates $60F_{254}$ (Merck, #1.05715.0001). Visualization was achieved by using UV light (254 nm) and appropriate reagent (ethanolic phosphomolybdic acid or *p*-anisaldehyde solution in H_2SO_4/AcOH/EtOH), followed by heating. Silica gel 60

(particle size 0.063-0.200 mm, Merck, #1.07734.9025) was used for silica gel open column chromatography. Silica gel 60 (spherical, particle size 0.04-0.05 mm, Kanto, #37562-84) was used for silica gel flash column chromatography. Silica gel 60N (neutral, particle size 0.063-0.200 mm, Kanto, #37563-79) was used for neutral silica gel open column chromatography. Chromatorex®-DIOL (particle size MB100-75/200, Fuji Silysia Chemical Ltd. HU50711) was used for Chromatorex DIOL silica gel open column chromatography. Chromatorex®-DIOL (particle size MB100-40/75, Fuji Silysia Chemical Ltd. HU50710) was used for Chromatorex DIOL silica gel flash column chromatography. Preparative TLC separations were carried out on 0.5 mm silica gel plates $60F_{254}$ (Merck). DIOL Preparative TLC separations were carried out on 0.25 mm DIOL silica gel plates (Fuji Silysia Chemical Ltd.). Dry THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Dry benzene, DMPU, DMF, toluene, Et_3N, DME, DMSO and diisopropylamine, were distilled from CaH_2. Celite (Hyflo Super-Cel Celite®) was purchased from Nacalai tesque Co., Inc. Florisil was purchased from Kanto Chemical Co., Inc. DISMIC®-13JP (disposable membrane filter unit, pore size 0.20 μm), purchased from Toyo Roshi Kaisha, Ltd., was used for 0.20 μm membrane filter. Lipase MY-30 was purchased from Meito Sangyo Co., Inc. All other commercially available reagents were used as received.

Ester ***4a***. A solution of LDA was prepared by slow addition of *n*-BuLi (1.60 M solution in hexane, 255 mL, 408 mmol) to a solution of dry diisopropylamine (55.0 mL, 416 mmol) in dry THF (682 mL) at –78 °C. To this solution was added dropwise DMPU (54.0 mL, 447 mmol) at –78 °C. After being stirred at –78 °C for 2 h, ethyl sorbate (47.8 g, 341 mmol) was added to this mixture. After being stirred at –78 °C for 2 h, the reaction mixture was allowed to warm up to room temperature. The reaction was

quenched with 10% acetic acid (700 mL, v/v). The aqueous layer was extracted with pentane. The combined organic layer was washed with H_2O (4x) and a saturated aqueous solution of $NaHCO_3$ (1x), dried over Na_2SO_4, and concentrated carefully under reduced pressure. The residue was purified by distillation to afford ester **4a** (31.4 g, bp 69-71 °C/15 mmHg, 66% yield) as a pale-yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were identical to those reported for this compound.[20] IR (KBr) ν_{max} 1736, 1653 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7 Hz, C*H*$_3$CH$_2$OC=O), 3.11 (2H, d, J = 7 Hz, C*H*$_2$C=O), 4.15 (2H, q, J = 7 Hz, CH$_3$C*H*$_2$OC=O), 5.06 (1H, d, J = 10 Hz, C*H*$_A$H$_B$=CH), 5.16 (1H, d, J = 17 Hz, CH$_A$*H*$_B$=CH), 5.79 (1H, dt, J = 15.5, 7 Hz, CH=C*H*CH$_2$C=O), 6.14 (1H, dd, J = 17, 15.5 Hz, C*H*=CHCH$_2$C=O), 6.34 (1H, ddd, J = 17, 17, 10 Hz, CH$_A$H$_B$=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 38.0, 60.7, 116.9, 125.7, 134.2, 136.3, 171.4.

*Carboxylic acid **4b***. To a solution of **4a** (31.4 g, 224 mmol) and EtOH (3 mL) in dry THF (450 mL) was added lithium hydroxide (1.0 M solution in H_2O, 270 mL, 269 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with 1.0 N HCl. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by neutral silica gel open column chromatography (hexane:EtOAc = 14:1 to 3:1) to afford carboxylic acid **4b** (24.8 g, 99% yield) as a yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were identical to those reported for this compound.[21] IR (KBr) ν_{max} 3021, 1709 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (2H, d, J = 7 Hz, C*H*$_2$C=O), 5.09 (1H, d, J = 10.5 Hz, C*H*$_A$H$_B$=CH), 5.19 (1H, d, J = 17 Hz, CH$_A$*H*$_B$=CH), 5.77 (1H, dt, J = 15.5, 7 Hz, CH=C*H*CH$_2$), 6.17 (1H, dd, J = 15.5, 10.5 Hz, C*H*=CHCH$_2$), 6.34 (1H, ddd, J = 17, 10.5, 10.5 Hz, CH$_A$H$_B$=C*H*). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 37.6, 117.4, 124.5, 134.9, 136.1, 178.1.

*Enol ester **5***. Carboxylic acid **4b** (1.00 g, 8.92 mmol) was dried azeotropically with toluene and dissolved in dry CH_2Cl_2 (50 mL). To this solution was added DMF (1 drop) followed by oxalyl chloride (1.30 mL, 15.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and concentrated under reduced pressure. The residue was diluted with dry CH_2Cl_2 (50 mL). This solution was added to a solution of 2-methyl-1,3-cyclopentanedione (770 mg, 6.86 mmol) and dry Et_3N (1.10 mL, 7.55 mmol) in dry CH_2Cl_2 (30 mL) at room temperature immediately via cannula. After being stirred at room temperature for 1 h, the reaction mixture was washed with H_2O (1x), a saturated aqueous solution of $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by neutral silica gel open column chromatography (hexane:EtOAc = 5:1) to afford enol ester **5** (1.18 g, 84% in 2 steps) as a yellow oil. IR (KBr) ν_{max} 1768, 1707, 1668, 1319, 1184, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H, t, J = 2 Hz, C*H*$_3$CC=O), 2.52 (2H, m, C*H* x2), 2.82 (2H, m, C*H* x2), 3.34 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$C=O), 5.12 (1H, d, J = 10 Hz, C*H*$_A$H$_B$=CH), 5.22 (1H, d, J = 17 Hz, CH$_A$*H*$_B$=CH), 5.79 (1H, dt, J = 15, 7.5 Hz, CH=C*H*CH$_2$C=O), 6.23 (1H, dd, J = 15, 10 Hz, C*H*=CHCH$_2$C=O), 6.35 (1H, ddd, J = 17, 10, 10 Hz, CH$_A$H$_B$=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6, 27.0, 34.3, 37.8, 117.9, 123.5, 126.3, 135.6, 135.9, 167.2, 175.6, 205.9. HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0835; found, 229.0843.

*Intramolecular Diels-Alder reaction of **5***. A solution of **5** (140 mg, 0.676 mmol) and BHT (5.6 mg, 0.027 mmol) in 1,2,4-trichlorobenzene (33 mL) was stirred at 200 °C for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel open column chromatography (hexane to EtOAc). This mixture

was purified by silica gel flash column chromatography (hexane:EtOAc = 4:1 to 3:1 to 2:1) to afford *endo*-**6** (92.0 mg, 66% yield) as a white solid and *exo*-**6** (25.9 mg, 19% yield) as a white solid. Relative stereochemistry of compound *endo*-**6** was determined by NOESY correlations (Figure 3). *endo*-**6**: IR (KBr) ν_{max} 1782, 1742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, s, CH_3CC=O), 1.89 (1H, ddd, J = 14, 7, 4 Hz, CH_AH$_B$CH$_2$C=O), 2.11-2.17 (2H, m, CH=CHCH_2), 2.22 (1H, dd, J = 14, 10.5 Hz, CH$_A$$H_BCH_2$C=O), 2.43-2.50 (2H, m, CH$_A$H$_B$CH_2C=O), 2.55 (1H, dd, J = 16.5, 14.5 Hz, CHCH_AH$_B$C=O), 2.71 (1H, dd, J = 16.5, 7 Hz, CHCH$_A$$H_B$C=O), 3.06 (1H, m, C$HCH_AH_B$C=O), 5.73 (1H, ddd, J = 9.5, 7, 3.5 Hz, CH=CHCH$_2$), 5.94 (1H, ddd, J = 9.5, 4.5, 2 Hz, CH=CHCH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 26.7, 32.6, 33.5, 35.8, 38.3, 50.2, 94.2, 124.9, 127.9, 175.1, 216.8. HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0835; found, 229.0845. mp: 98-99 °C. *exo*-**6**: IR (KBr) ν_{max} 1774, 1743, 1237 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, s, CH_3CC=O), 1.96 (1H, dd, J = 17.5, 4 Hz, CH=CHCH_AH$_B$), 2.08 (1H, m, CH=CHCH$_A$$H_B$), 2.17 (1H, m, C$H_AH_BCH_2$C=O), 2.31 (1H, ddd, J = 14, 9, 3 Hz, CH$_A$$H_BCH_2$C=O), 2.41 (1H, dd, J = 17.5, 10.5 Hz, CHCH_AH$_B$C=O), 2.48-2.57 (2H, m, CH$_A$H$_B$CH_2C=O), 2.85 (1H, dd, J = 17.5, 10 Hz, CHCH$_A$$H_B$C=O), 2.95 (1H, m, C$HCH_AH_B$C=O), 5.75-5.78 (2H, m, CH=CHCH$_A$H$_B$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 31.66, 31.69, 33.9, 35.6, 38.1, 50.7, 91.6, 124.0, 125.6, 174.8, 216.3. HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0835; found, 229.0836. mp: 87-89 °C.

*Decagram-scale synthesis of endo-**6** from carboxylic acid **4b**.* To a solution of **4b** (24.8 g, 221 mmol) in dry CH_2Cl_2 (1.5 L) was added DMF (0.05 mL) followed by oxalyl chloride (32.0 mL, 376 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and concentrated under reduced pressure. The residue was

diluted with dry CH_2Cl_2 (100 mL). This solution was added to a solution of 2-methyl-1,3-cyclopentanedione (19.1 g, 170 mmol) and dry Et_3N (26.1 mL, 187 mmol) in dry CH_2Cl_2 (850 mL) at room temperature immediately via cannula. After being stirred at room temperature for 1 h, the reaction mixture was washed with H_2O (1x), a saturated aqueous solution of $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a column with neutral silica gel (hexane:EtOAc = 4:1) to afford enol ester **5** (27.6 g, contained about 8% of carboxylic acid **4b**) as a yellow oil. A solution of **5** (27.6 g, 134 mmol) and BHT (1.20 g, 5.45 mmol) in 1,2,4-trichlorobenzene (1340 mL) was stirred at 155 °C for 10 h. The reaction mixture was concentrated under reduced pressure at 83 °C (7 mmHg). The residue was purified by silica gel open column chromatography (hexane to EtOAc) to give an 83:17 mixture of *endo*-**6** and *exo*-**6**. This mixture was purified by recrystallization from hexane/EtOAc and silica gel open column chromatography (hexane:EtOAc = 2:1) to afford *endo*-**6** (16.4 g, 34% yield in 3 steps) as a white solid and *exo*-**6** (3.68 g, 8% yield in 3 steps) as a white solid.

*Reduction of endo-**6**.* To a solution of *endo*-**6** (8.87 g, 43.0 mmol) in MeOH (717 mL) was added $NaBH_4$ (3.38 g, 89.3 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched with acetic acid and the reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O and the aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 3:2) to afford major isomer (±)-**7** (7.33 g, 82% yield) as a white solid and minor isomer (±)-*epi*-**7** (788 mg, 9% yield) as a white solid. Relative stereochemistry of (±)-**7** was determined by

NOESY correlations (Figure 3). (±)-**7**: IR (KBr) ν_{max} 3433, 1773, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s, CH_3CCOH), 1.38 (1H, m, $CH_AH_BCH_AH_BCHOH$), 1.56 (1H, m, $CH_AH_BCH_AH_BCHOH$), 1.73 (1H, dd, J = 18.5, 2.5 Hz, CH=CHCH_AH_B), 2.02-2.14 (2H, m, $CH_AH_BCH_AH_BCHOH$), 2.43 (1H, dd, J = 16, 14 Hz, CHCH_AH_BC=O), 2.54 (1H, ddd, J = 18.5, 4, 2 Hz, CH=CHCH_AH_B), 2.61 (1H, dd, J = 16, 7 Hz, $CHCH_AH_BC$=O), 2.95 (1H, ddd, J = 14, 7, 2 Hz, CHCH_AH_BC=O), 4.13 (1H, dd, J = 9, 8 Hz, CHOH), 5.77-5.85 (2H, m, CH=CHCH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 29.5, 29.9, 31.4, 32.7, 39.6, 46.9, 78.2, 96.1, 124.1, 130.0, 176.5. HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{16}O_3Na$, 231.0992; found, 231.1002. mp: 93-94 °C. (±)-*epi*-**7**: IR (KBr) ν_{max} 3485, 1754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, s, CH_3CCOH), 1.76-1.89 (3H, m, CH x3), 1.99-2.11 (3H, m, CH x3), 2.44 (1H, dd, J = 16, 14.5 Hz, CHCH_AH_BC=O) 2.64 (1H, dd, J = 16, 7 Hz, $CHCH_AH_BC$=O), 2.96 (1H, m, CHCH_AH_BC=O), 3.78 (1H, d, J = 4 Hz, CHOH), 5.74 (1H, m, CH=CHCH_2). 5.84 (1H, ddd, J = 10, 4, 2.5 Hz, CH=CHCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 31.1, 31.7, 33.1, 38.4, 39.3, 48.3, 81.3, 97.2 124.3, 129.3, 175.9. HRMS (ESI) $[M+Na]^+$ calcd for $C_{12}H_{16}O_3Na$, 231.0992; found, 231.0983. mp: 112-113°C.

Optical resolution of alcohol (±)-*7*. To a solution of racemic alcohol (±)-**7** (6.24 g, 30.0 mmol) in dry DME/toluene (278 mL, 1:4) were added vinyl acetate (52.3 g, 608 mmol) and lipase MY-30 (11.35 g) at room temperature. After being stirred at room temperature for 13 h, to the resulting mixture was added lipase MY-30 (11.33 g) at room temperature. After being stirred at room temperature for 10.5 h, to the resulting mixture was added lipase MY-30 (11.09 g) at room temperature. After being stirred at room temperature for 16 h, to the resulting mixture was added lipase MY-30 (11.02 g) at room temperature. After being stirred at room temperature for 7.5 h, the reaction

mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel open column chromatography (hexane:EtOAc = 2:1) to afford acetate **8** (3.50 g, 47% yield, 90% ee) as a white solid and alcohol **7** (3.10 g, 50% yield, 89% ee) as a white solid. Recrystallization from hexane/CH_2Cl_2 afforded **8** (1.92 g, 99% ee, 55% yield) as a white solid. Recrystallization from hexane/EtOAc afforded **7** (77%, >99% ee) as a white solid. Enantiomeric excess was determined by chiral HPLC analysis. Chiral HPLC analysis for **8** (CHIRALPAK IB column, hexane/2-propanol = 90/10, flow rate = 0.5 mL/min, detection 220 nm light, 30 °C) t_R = 17.7 min (major isomer), 19.1 min (minor isomer). Chiral HPLC analysis for **7** (CHIRALPAK IB column, hexane/2-propanol = 90/10, flow rate = 0.5 mL/min, detection 220 nm light, 30 °C) t_R = 20.9 min (minor isomer), 22.1 min (major isomer). Absolute stereochemistry of **8** was determined by X-ray crystallographic analysis. acetate **8**: IR (KBr) ν_{max} 1772, 1734, 1064, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, s, C*H*$_3$CCCH$_2$), 1.40 (1H, m, C*H*), 1.60 (1H, ddd, *J* = 14.5, 9, 8 Hz, C*H*), 1.84 (1H, dq, *J* = 19, 3 Hz, C*H*), 2.05 (3H, s, C*H*$_3$C=O), 2.10 (1H, m, C*H*), 2.30 (1H, m, C*H*), 2.43 (1H, dd, *J* = 16, 14.5 Hz, C*H*), 2.48 (1H, m, C*H*), 2.61 (1H, dd, *J* = 16, 7 Hz, C*H*), 2.94 (1H, m, C*H*), 5.01 (1H, t, *J* = 8.5 Hz, C*H*OAc), 5.74-5.86 (2H, m, C*H*=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 21.0, 27.0, 29.9, 32.8, 33.1, 39.1, 46.2, 80.1, 95.0, 124.0, 129.3, 170.6, 175.9. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.16; H, 7.50. mp: 123-124 °C. $[\alpha]_D^{29}$ +5.3 (*c* 0.17, $CHCl_3$). alcohol **7**: $[\alpha]_D^{24}$ +4.1 (*c* 0.85, $CHCl_3$).

*Mizoroki–Heck reaction of **8***. To a solution of **8** (2.00 g, 7.94 mmol) and **9**[12] (4.41 g, 11.9 mmol) in dry DMF (40 mL) was added NaOAc (725 mg, 8.84 mmol) under Ar atmosphere. The resulting mixture was degassed by three freeze-thaw cycles, and the

flask was filled with Ar. After being heated to 50 °C, to this solution was added palladacycle **10** (133 mg, 0.142 mmol). After being heated to 130 °C, the resulting mixture was stirred for 2 h. The reaction mixture was cooled to room temperature and filtered through Florisil. The filtrate was washed with H_2O (1x) and brine (1x), and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 5:1 to 3:1 to 1:1) to afford **11a** (2.99 g, 70% yield, dr = >95:<5 determined by ^{1}H NMR analysis) as a yellow solid and **12a** (842 mg, 20% yield, dr = >95:<5 determined by ^{1}H NMR analysis) as a yellow solid. Relative stereochemistry of **11a** was determined by comparison of ^{1}H NMR spectra of lactol **13** prepared from alcohol **11b** whose relative stereochemistry was determined by NOESY correlations (Figure 4). Relative stereochemistry of **12a** was determined by comparison of ^{1}H NMR spectra of acetate **12a** prepared from alcohol **12b** whose relative stereochemistry was determined by NOESY correlations (Figure 4). **11a**: IR (KBr) ν_{max} 1781, 1740, 1509, 1069, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, s, C*H*$_3$CCCH), 1.43 (1H, m, C*H*), 1.69 (1H, m, C*H*), 2.03-2.36 (5H, m, C*H* x5), 2.11 (3H, s, C*H*$_3$C=O), 3.26 (1H, d, *J* = 10 Hz, C*H*), 5.08 (1H, t, *J* = 8.5 Hz, C*H*OAc), 5.16 (2H, s, C*H*$_2$ of Bn), 5.17 (2H, s, C*H*$_2$ of Bn), 5.66 (1H, dd, *J* = 10.5, 1.5 Hz, C*H*=CH), 5.78 (1H, dd, *J* = 10.5, 2.5 Hz, CH=C*H*), 6.64 (1H, br s, aryl H-2), 6.66 (1H, dd, *J* = 8, 2 Hz, aryl H-6), 6.89 (1H, d, *J* = 8 Hz, aryl H-5), 7.28-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.0, 26.9, 28.1, 32.1, 44.7, 44.8, 48.9, 71.3, 71.6, 79.4, 92.3, 115.1, 115.2, 120.3, 127.3, 127.4, 127.9, 128.0, 128.5, 130.9, 131.0, 134.6, 137.1, 137.2, 148.4, 148.8, 170.5, 175.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{34}H_{34}O_6Na$, 561.2248; found, 561.2230. mp: 42-44 °C. $[\alpha]_D^{29}$ +83.2 (*c* 0.87, $CHCl_3$). **12a**: IR (KBr) ν_{max} 1748, 1511, 1024 cm^{-1}. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 0.66 (3H, s, C*H*$_3$CCCH), 1.59 (1H, m, C*H*), 1.80 (1H, m, C*H*), 1.89-1.97 (2H, m, C*H* x2), 2.02 (3H, s, C*H*$_3$C=O), 2.34-2.51 (2H, m, C*H* x2), 2.86 (1H, ddd, *J* = 17, 7.5, 2 Hz, C*H*), 2.98 (1H, dd, *J* = 17, 6 Hz, C*H*), 3.38 (1H, ddd, *J* = 11, 7.5, 6.5 Hz, C*H*), 5.05 (1H, dd, *J* = 7.5, 7 Hz, C*H*OAc), 5.13 (1H, d, *J* = 12 Hz, C*H*$_A$H$_B$ of Bn), 5.14 (2H, s, C*H*$_2$ of Bn), 5.18 (1H, d, *J* = 12 Hz, CH$_A$*H*$_B$ of Bn), 5.84 (1H, d, *J* = 1.5 Hz, C=C*H*C=O), 6.74 (1H, dd, *J* = 8, 2 Hz, aryl H-6), 6.76 (1H, br s, aryl H-2), 6.86 (1H, d, *J* = 8 Hz, aryl H-5), 7.27-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.1, 28.8, 30.9, 34.4, 37.2, 38.0, 51.5, 71.3, 71.7, 83.3, 95.3, 114.8, 115.0, 115.8, 119.7, 127.25, 127.31, 127.85, 127.89, 128.49, 128.51, 137.1, 137.7, 147.9, 148.7, 170.3, 172.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{34}H_{34}O_6Na$, 561.2248; found, 561.2275. mp: 44-46 °C. $[\alpha]_D^{29}$ –101 (*c* 0.71, $CHCl_3$).

Mizoroki–Heck reaction of alcohol (±)-7. To a solution of alcohol (±)-**7** (315 mg, 1.51 mmol, racemate) and **9** (899 mg, 2.43 mmol) in dry DMF (7.6 mL) was added NaOAc (138 mg, 1.68 mmol) under Ar atmosphere. The resulting mixture was degassed by three freeze-thaw cycles, and the flask was filled with Ar. After being heated to 50 °C, to this solution was added palladacycle **10** (155 mg, 0.165 mmol). After being heated to 130 °C, the resulting mixture was stirred for 5 h. The reaction mixture was cooled to room temperature and then filtered through Florisil. The filtrate was washed with H_2O (1x) and brine (1x), and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 3:1 to 2:1 to 1:1) to afford major product **11b** (462 mg, 62% yield, dr = >95:<5 determined by ^{1}H NMR analysis) as a white solid and minor product **12b** (208 mg, 28% yield, dr = >95:<5 determined by ^{1}H NMR analysis) as a white solid. Relative stereochemistry of compounds **11b** and **12b** was determined by NOESY correlations

(Figure 4). **11b**: IR (KBr) ν_{max} 3446, 1776, 1509, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ1.19 (3H, s, CH_3), 1.43 (1H, dddd, J = 12.5, 11, 9, 8 Hz, $CH_AH_BCH_AH_BCHOH$), 1.63 (1H, ddd, J = 14.5, 9, 8 Hz, $CH_AH_BCH_AH_BCHOH$), 2.02-2.30 (5H, m, $CH_AH_BCH_AH_BCHOH$, CHCH_2C=O), 3.27 (1H, br d, J = 9.5 Hz, ArCH), 4.16 (1H, dd, J = 8, 8 Hz, CHOH), 5.16 (2H, s, CH_2 of Bn), 5.17 (2H, s, CH_2 of Bn), 5.67 (1H, dd, J = 10, 1.5 Hz, CHCH=CH), 5.82 (1H, dd, J = 10, 2 Hz, CHCH=CH), 6.65 (1H, br s, aryl H-6), 6.66 (1H, dd, J = 8.5, 2 Hz, aryl H-2), 6.89 (1H, d, J = 8.5 Hz, aryl H-5), 7.28-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 27.8, 29.6, 32.1, 44.9, 45.1, 49.5, 71.3, 71.5, 78.0, 93.2, 115.1, 115.2, 120.3, 127.3, 127.4, 127.8, 127.9, 128.5, 130.5, 130.9, 134.8, 137.1, 137.2, 148.2, 148.8, 175.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{32}O_5Na$, 519.2142; found, 519.2159. mp:148-149 °C. **12b**: IR (KBr) ν_{max} 3447, 1747, 1512, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.46 (3H, s, CH_3), 1.67 (1H, dd, J = 15, 5.5 Hz, ArCHCH_AH_BCCH_3), 1.73-1.93 (2H, m, C$H_AH_BCH_AH_B$CHOH), 2.00 (1H, dd, J = 15, 5 Hz, ArCHCH_AH_BCCH_3), 2.23-2.45 (2H, m, $CH_AH_BCH_AH_B$CHOH), 2.80 (1H, ddd, J = 16, 7.5, 1.5 Hz, ArCHCH_AH_BC=C), 3.09 (1H, dd, J = 16, 4 Hz, ArCHCH_AH_BC=C), 3.44 (1H, m, ArCH), 4.11 (1H, t, J = 7.5 Hz, CH_3CCHOH), 5.13 (2H, s, CH_2 of Bn), 5.13 (1H, d, J = 12 Hz, CH_AH_B of Bn), 5.17 (1H, d, J = 12 Hz, CH_AH_B of Bn), 5.83 (1H, d, J = 1.5 Hz, C=CHC=O), 6.73 (1H, dd, J = 8, 1.5 Hz, aryl H-6), 6.77 (1H, d, J = 1.5 Hz, aryl H-2), 6.83 (1H, d, J = 8 Hz, aryl H-5), 7.27-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 29.8, 30.1, 32.6, 35.6, 37.3, 52.0, 71.3, 71.5, 81.7, 96.0, 114.77, 114.81, 115.3, 119.4, 127.28, 127.31, 127.78, 127.80, 128.45, 128.51, 137.17, 137.21, 137.6, 147.5, 148.5, 170.8, 172.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{32}O_5Na$, 519.2142; found, 519.2154. mp:152-153 °C.

*Lactol **13***. Lactone **11a** (1.83 g, 3.40 mmol) was dried azeotropically with toluene/CH_2Cl_2 (1:1) and dissolved in dry CH_2Cl_2 (85 mL). To this solution was added dropwise DIBAL (1.00 M solution in toluene, 8.50 mL, 8.50 mmol) at –78 °C. After being stirred at –78 °C for 1 h, the reaction was quenched with 1 N HCl. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel open column chromatography (CH_2Cl_2:THF = 4:1) to afford lactol **13** (1.51 g, 90% yield, dr = 80:20 determined by ^{1}H NMR analysis) as a white solid. IR (KBr) ν_{max} 3427, 1638 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.99 (2.4H, s, C*H*$_3$), 1.05 (0.6H, s, C*H*$_3$), 1.12-1.37 (1.2H, m), 1.43 (0.8H, td, *J* = 12, 6 Hz), 1.59-2.02 (5H, m), 3.20 (0.2H, br d, *J* = 11 Hz), 3.26 (0.8H, br d, *J* = 10.5 H), 3.88 (1H, m), 4.80 (1H, d, *J* = 5 Hz), 5.07 (1H, d, *J* = 12 Hz, C*H*$_A$H$_B$ of Bn), 5.09 (2H, s, C*H*$_2$ of Bn), 5.13 (1H, d, *J* = 12 Hz, CH$_A$*H*$_B$ of Bn), 5.23 (1H, m), 5.49 (0.8H, d, *J* = 10.5 Hz, C*H*=CH), 5.52 (0.2H, d, *J* = 10.5 Hz, C*H*=CH), 5.70 (0.8H, dd, *J* = 10.5, 1.5 Hz, CH=C*H*), 5.74 (0.2H, dd, *J* = 10.5, 1.5 Hz, CH=C*H*), 5.84 (0.2H, d, *J* = 6 Hz, O*H*), 6.19 (0.8H, d, *J* = 4 Hz, O*H*), 6.65-6.73 (1H, m, aryl H-6), 6.84 (0.8H, d, *J* = 1.5 Hz, aryl H-2), 6.88 (0.2H, d, *J* = 1.5 Hz, aryl H-2), 6.99 (0.8H, d, *J* = 8 Hz, aryl H-5), 7.01 (0.2H, d, *J* = 7.5 Hz, aryl H-5), 7.27-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 18.2, 18.3, 28.9, 29.2, 29.7, 29.9, 35.9, 42.8, 44.7, 44.9, 46.3, 49.4, 49.6, 70.2, 70.3, 77.4, 77.5, 88.2, 89.5, 95.7, 97.8, 114.4, 114.6, 114.7, 119.8, 127.5, 127.65, 127.70, 128.30, 128.35, 130.3, 131.8, 132.2, 136.8, 137.0, 137.3, 137.4, 137.5, 146.9, 148.07, 148.13. Anal. Calcd for $C_{32}H_{34}O_5$: C, 77.08; H, 6.87. Found: C, 76.73; H, 6.83. mp: 62-63 °C.

*Tetracycle **14***. To a solution of **13** (1.35 g, 2.71 mmol) in MeOH (45 mL) was

added $Sc(OTf)_3$ (269 mg, 0.547 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 min, and then heated to reflux. After being stirred at reflux for 45 h, the reaction mixture was cooled to room temperature. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (4x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 1:1) to afford tetracycle **14** (1.10 g, 85% yield) as a white solid. IR (KBr) ν_{max} 3397, 1505, 1275, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s, C*H*$_3$), 1.38 (1H, ddd, *J* = 20.5, 10.5, 10.5 Hz, CH_AH_BC*H*$_A$$H_B$CHOH), 1.56 (1H, m, C*H*$_A$$H_B$$CH_AH_B$CHOH), 2.02-2.19 (2H, m, CH_A*H*$_B$$CH_A$*H*$_B$CHOH), 2.26 (1H, br d, *J* = 15 Hz, COHC*H*), 3.25 (1H, br d, *J* = 15 Hz, COHCHC*H*), 4.18 (1H, m, CH_3CC*H*OH), 5.14 (2H, s, C*H*$_2$ of Bn), 5.16 (1H, d, *J* = 12 Hz, C*H*$_A$$H_B$ of Bn), 5.21 (1H, d, *J* = 12 Hz, CH_A*H*$_B$ of Bn), 5.78 (1H, dd, *J* = 10.5, 2.5 Hz, CH_3CC*H*=CH), 6.20 (1H, d, *J* = 10.5 Hz, CH_3CCH=C*H*), 6.23 (1H, d, *J* = 9.5 Hz, COHCHC*H*=CH), 6.51 (1H, dd, *J* = 9.5, 2.5 Hz, COHCHCH=C*H*), 6.78 (1H, s, aryl H-4), 7.00 (1H, s, aryl H-1), 7.27-7.49 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 30.0, 30.8, 39.6, 42.6, 50.7, 71.7, 72.0, 78.9, 81.0, 111.5, 114.2, 125.1, 127.3, 127.4, 127.5, 127.7, 127.77, 127.84, 128.3, 128.45, 128.48, 128.9, 130.7, 130.8, 137.4, 147.4, 148.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{32}O_4Na$, 503.2193; found, 503.2181. mp: 57-59 °C. $[\alpha]_D^{28}$ –63.9 (*c* 0.86, $CHCl_3$).

*Alcohol **15***. To a solution of **14** (1.07 g, 2.24 mmol) in dry CH_2Cl_2 (22.4 mL) was added Crabtree catalyst (174 mg, 0.216 mmol) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 20 h, and then filtered through Florisil. The resulting mixture was concentrated under reduced

pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 1:2) to afford alcohol **15** (707 mg, 65% yield) as a pale yellow solid. IR (KBr) ν_{max} 3434, 1636, 1507 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.01 (3H, s, C*H*$_3$), 1.14-1.50 (5H, m, $CH_3CCH_AH_BCH_AH_B$, COHC*H*CH_AH_B, C*H*$_2CH_AH_BCHOH$), 1.50-1.65 (2H, m, $CH_3CCH_AH_B$, CH_AH_BCHOH), 1.99-2.24 (4H, m, $CH_3CCH_AH_BCH_AH_B$, $COHCHCH_AH_B$, CH_AH_BCHOH), 2.37 (1H, t, J = 11.5 Hz, COHCHC*H*), 2.73 (2H, dd, J = 9.5, 3 Hz, $COHCHCH_AH_BCH_2$), 4.19 (1H, dd, J = 9, 8 Hz, CH_3CCHOH), 5.03 (2H, s, C*H*$_2$ of Bn), 5.04 (2H, s, C*H*$_2$ of Bn), 6.69 (1H, s, aryl H-4), 6.91 (1H, s, aryl H-1), 7.24-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, CD_3OD) δ 17.3, 23.7, 27.2, 28.8, 29.5, 30.0, 30.9, 41.5, 45.8, 48.5, 72.4, 72.9, 81.5, 84.5, 114.9, 116.7, 128.7, 128.8, 129.38, 129.39, 131.3, 134.5, 139.0, 139.1, 148.1, 148.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{36}O_4Na$, 507.2506; found, 507.2525. mp: 65-66 °C. $[\alpha]_D^{29}$ +47.2 (*c* 0.25, MeOH).

*Ketone **16***. To a solution of **15** (787 mg, 1.63 mmol) in dry DMSO (33.0 mL) was added IBX (690 mg, 2.46 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel open column chromatography (hexane:EtOAc = 1:1) to afford ketone **16** (681 mg, 87% yield) as a white solid. IR (KBr) ν_{max} 3455, 1730, 1507, 1243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, s, C*H*$_3$), 1.28-1.70 (5H, m, C*H* x5), 1.86 (1H, m, C*H*), 2.14-2.27 (3H, m, C*H* x3), 2.43-2.61 (3H, m, C*H* x3), 2.78-2.88 (2H, m, C*H* x2), 5.11 (2H, s, C*H*$_2$ of Bn), 5.12 (2H, s, C*H*$_2$ of Bn), 6.70 (1H, s, aryl), 6.87 (1H, s, aryl), 7.27-7.48 (10H, m,

Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 22.1, 25.7, 26.7, 29.7, 32.1, 33.2, 40.1, 44.8, 53.4, 71.3, 72.0, 81.9, 113.7, 115.4, 127.3, 127.4, 127.8, 128.5, 129.6, 131.8, 137.4, 137.5, 147.1, 147.6, 220.9. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_4Na$, 505.2349; found, 505.2347. mp: 94-95 °C. $[\alpha]_D^{26}$ +79.5 (*c* 0.66, $CHCl_3$).

*Enone **17a***. To a solution of **16** (667 mg, 1.38 mmol) in dry CH_2Cl_2 (46 mL) were added dry Et_3N (3.9 mL, 28 mmol) and TMSOTf (2.5 mL, 14 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with pentane/Et_2O (9:1, 2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure to afford silyl enol ether, which was used for the next reaction without further purification. The crude silyl enol ether was dried azeotropically with benzene (3x), and dissolved in dry DMSO (17.3 mL). To this solution was added $Pd(OAc)_2$ (64.0 mg, 0.285 mmol). The reaction mixture was stirred under atmosphere of oxygen (1 atm) at 60 °C for 2.5 h, and then the reaction mixture was cooled to room temperature. The reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 8:1) to afford enone **17a** (668 mg, 88% yield in 2 steps) as a colorless oil. IR (KBr) ν_{max} 1714, 1508 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (9H, s, OSi(C*H*$_3$)$_3$), 1.05 (3H, s, C*H*$_3$CC=O), 1.24-1.41 (2H, m, C*H*$_A$H$_B$CHCOTMS), 1.67 (1H, ddd, *J* = 14.5, 6.5, 6.5 Hz, $CH_3CCH_2CH_AH_B$), 1.76-1.94 (2H, m, C*H*COTMS, C*H*), 2.03-2.20 (2H, m, C*H*-CHCOTMS, C*H*), 2.27 (1H, dd, *J* = 11.5, 2.5 Hz, CH$_A$*H*$_B$CHCOTMS), 2.65-2.80 (2H, m, C*H*$_2$CH$_A$H$_B$CHCOTMS), 5.05 (1H, d, *J* = 11.5 Hz, C*H*$_A$H$_B$ of Bn), 5.07 (1H, d, *J* =

11.5 Hz, CH_AH_B of Bn), 5.10 (2H, s, CH_2 of Bn), 6.25 (1H, d, J = 6 Hz, CH=C*H*C=O), 6.63 (1H, s, aryl H-4), 6.70 (1H, s, aryl H-1), 7.27-7.59 (11H, m, C*H*=CHC=O, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.7, 20.7, 23.9, 27.5, 29.4, 29.8, 34.8, 45.7, 53.5, 71.4, 71.6, 86.6, 114.2, 114.9, 127.27, 127.33, 127.7, 128.4, 129.1, 132.8, 133.1, 137.4, 137.5, 147.0, 147.3, 160.2, 211.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{35}H_{40}O_4SiNa$, 575.2588; found, 575.2583. $[\alpha]_D^{29}$ +116 (*c* 0.32, $CHCl_3$).

*Enone **17b***. To a solution of enone **17a** (653 mg, 1.18 mmol) in dry THF (12.0 mL) was added TBAF (1.0 M solution in THF, 1.80 mL, 1.80 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel open column chromatography (CH_2Cl_2:EtOAc = 8:1) to afford hydroxy enone **17b** (552 mg, 97% yield) as a white solid. ^{1}H and ^{13}C NMR data were identical to those reported for this compound.[7] IR (KBr) ν_{max} 3450, 1711, 1508, 1265 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s, CH_3), 1.29-1.44 (2H, m, C*H* x2), 1.67 (1H, ddd, J = 14.5, 8, 8 Hz, C*H*), 1.78-1.92 (2H, m, C*H* x2), 2.07-2.23 (2H, m, C*H* x2), 2.39 (1H, m, C*H*), 2.68-2.81 (2H, m, C*H* x2), 5.05 (1H, d, J = 12 Hz, CH_AH_B of Bn), 5.09 (1H, d, J = 12 Hz, CH_AH_B of Bn), 5.10 (2H, s, CH_2 of Bn), 6.27 (1H, d, J = 6 Hz, C*H*=CH), 6.63 (1H, s, aryl), 6.69 (1H, s, aryl), 7.27-7.47 (11H, m, CH=C*H*, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 23.8, 27.2, 28.7, 29.7, 34.9, 44.8, 52.9, 71.3, 71.6, 83.4, 114.3, 114.9, 127.3, 127.4, 127.7, 128.4, 129.1, 132.9, 133.1, 137.40, 137.43, 147.1, 147.3, 160.1, 211.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{32}O_4Na$, 503.2193; found, 503.2178. mp: 163-164 °C. $[\alpha]_D^{29}$ +178 (*c* 0.57, $CHCl_3$) [lit.[7] $[\alpha]_D^{23}$ +165.8 (*c* 1.0, $CHCl_3$)].

*Reduction of enone **17b**.* To a solution of enone **17b** (529 mg, 1.10 mmol) in MeOH/dry THF (14.6 mL, 1:1) were added $CeCl_3 \cdot 7H_2O$ (827 mg, 2.22 mmol) and $NaBH_4$ (229 mg, 6.04 mmol) at room temperature. After being stirred at room temperature for 30 min, to the resulting mixture was added $NaBH_4$ (44.6 mg, 1.19 mmol) at room temperature. After being stirred at room temperature for 25 min, to the resulting mixture was added $NaBH_4$ (9.8 mg, 0.26 mmol) at room temperature. After being stirred at room temperature for 20 min, the resulting mixture was poured into water. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 1:1) to afford major isomer **18** (426 mg, 80% yield) as a white solid and minor isomer *epi*-**18** (46.7 mg, 9% yield) as a white solid. ^{1}H NMR, ^{13}C NMR and IR data were identical to those reported for these compounds.[7] **18**: IR (KBr) ν_{max} 3346, 1506, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, s, C*H*$_3$), 1.28 (1H, m, C*H*), 1.44-1.75 (4H, m, C*H* x4), 2.11 (1H, ddd, J = 13, 7, 3 Hz, C*H*), 2.19-2.33 (2H, m, C*H* x2), 2.73-2.86 (2H, m, C*H* x2), 4.81 (1H, s, CH_3CCHOH), 5.12 (4H, s, C*H*$_2$ of Bn), 6.00 (1H, d, J = 5.5 Hz, C*H*=CH), 6.06 (1H, dd, J = 5.5, 1.5 Hz, CH=C*H*), 6.69 (1H, s, aryl), 6.90 (1H, s, aryl), 7.27-7.50 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 23.0, 27.0, 29.9, 31.8, 40.5, 44.5, 49.8, 71.3, 72.0, 84.3, 85.9, 114.2, 115.3, 127.3, 127.4, 127.7, 128.40, 128.42, 130.1, 132.3, 133.6, 137.5, 137.6, 139.4, 147.0, 147.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_4Na$, 505.2349; found, 505.2365. mp: 73-75 °C. $[\alpha]_D^{27}$ +61.1 (*c* 0.98, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ +50.8 (*c* 0.93, $CHCl_3$)]. *epi*-**18**: IR (KBr) ν_{max} 3425, 1508 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, s, C*H*$_3$), 1.24-1.55 (3H, m, C*H* x3), 1.57-1.69 (2H, m, C*H* x2), 2.04 (1H, m, C*H*), 2.22 (1H, br t,

J = 10.5 Hz, C*H*), 2.30 (1H, m, C*H*), 2.73-2.83 (2H, m, C*H* x2), 4.01 (1H, br s, C*H*OH), 5.10 (2H, s, CH_2 of Bn), 5.12 (2H, s, CH_2 of Bn), 6.20 (1H, dd, *J* = 6, 2.5 Hz, C*H*=CH), 6.23 (1H, d, *J* = 6 Hz, CH=C*H*), 6.69 (1H, s, aryl), 6.86 (1H, s, aryl), 7.26-7.49 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 23.2, 27.8, 29.9, 36.2, 39.6, 43.6, 46.8, 71.3, 72.0, 83.7, 86.0, 114.3, 115.3, 127.3, 127.4, 127.7, 128.40, 128.43, 130.2, 132.2, 137.0, 137.5, 137.6, 138.5, 147.0, 147.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_4Na$, 505.2349; found, 505.2341. mp: 127-128 °C. $[\alpha]_D^{29}$ +109 (*c* 0.98, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ +116.3 (*c* 0.435, $CHCl_3$)].

*Dihydroxylation of **18**.* To a solution of **18** (100 mg, 0.207 mmol) in acetone (6.9 mL) and *t*-BuOH (67 μL) were added OsO_4 (4% aqueous solution, w/v, 0.18 mL, 0.029 mmol) and NMO (106 mg, 0.907 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous solution of $NaHSO_3$. The aqueous layer was extracted with EtOAc (5x). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (hexane:EtOAc = 1:1 to 1:3) to afford minor product **19a** (18.7 mg, 17% yield) as a white solid and major product **19b** (45.3 mg, 42% yield) as a white solid. **19a**: IR (KBr) ν_{max} 3419, 1638, 1458, 1261 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s, CH_3), 1.30 (1H, ddd, *J* = 13.5, 13.5, 3 Hz, C*H*), 1.42-1.67 (2H, m, C*H* x2), 1.76 (1H, td, *J* = 13.5, 3.5 Hz, C*H*), 1.91 (1H, ddd, *J* = 12, 11.5, 6.5 Hz, C*H*), 2.12-2.25 (2H, m, C*H* x2), 2.71-2.90 (2H, m, C*H* x2), 3.28 (1H, td, *J* = 11.5, 3.5 Hz, C*H*), 4.11 (1H, d, *J* = 6.5 Hz, C*H*OH), 4.12 (1H, d, *J* = 8 Hz, C*H*OH), 4.33 (1H, dd, *J* = 8, 6.5 Hz, CH_3CHOHC*H*OH), 5.11 (4H, s, CH_2 of Bn), 6.69 (1H, s, aryl), 6.88 (1H, s, aryl), 7.27-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 22.6, 25.2, 28.4,

29.9, 38.2, 45.6, 46.4, 68.9, 71.5, 72.1, 77.6, 79.1, 82.0, 113.4, 115.6, 127.4, 127.5, 127.7, 128.4, 129.6, 134.1, 137.6, 137.7, 147.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{36}O_6Na$, 539.2404; found, 539.2402. mp: 160-161 °C. $[\alpha]_D^{30}$ +45.4 (*c* 0.21, $CHCl_3$) [lit.[7] $[\alpha]_D^{19.5}$ +52.8 (*c* 0.22, $CHCl_3$)]. **19b**: IR (KBr) ν_{max} 3419, 1518, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ1.10 (3H, s, C*H*$_3$), 1.15-1.37 (2H, m, C*H* x2), 1.43 (1H, m, C*H*), 1.57 (1H, t, *J* = 12 Hz, C*H*), 1.71 (1H, d, *J* = 13.5 Hz, C*H*), 2.03-2.19 (2H, m, C*H* x2), 2.45 (1H, br t, *J* = 11 Hz, C*H*), 2.67-3.14 (2H, m, C*H* x2), 4.02 (1H, d, *J* = 6 Hz, C*H*OH), 4.10 (1H, dd, *J* = 8.5, 6 Hz, CH_3CHOHC*H*OH), 4.25 (1H, d, *J* = 8.5 Hz, C*H*OH), 5.07 (2H, s, C*H*$_2$ of Bn), 5.09 (2H, s, C*H*$_2$ of Bn), 6.66 (1H, s, aryl), 6.89 (1H, s, aryl), 7.27-7.46 (10H, m, Ph of Bn). ^{13}C NMR (150 MHz, $CDCl_3$) δ16.8, 22.4, 25.9, 29.7, 29.75, 29.80, 39.6, 43.9, 67.2, 71.2, 72.1, 74.5, 80.2, 86.3, 113.9, 115.2, 127.3, 127.4, 127.7, 127.8, 128.4, 129.9, 132.0, 137.3, 137.5, 146.9, 147.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{36}O_6Na$, 539.2404; found, 539.2417. mp: 157-158 °C. $[\alpha]_D^{30}$ +44.1 (*c* 0.52, $CHCl_3$) [lit.[7] $[\alpha]_D^{19.5}$ +45.6 (*c* 0.835, $CHCl_3$)].

*15,16-cis-Diol **1a**.* To a solution of **19a** (6.6 mg, 0.013 mmol) in EtOAc (1.3 mL) was added Pd/$BaSO_4$ (5%, 14.8 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 7.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (CH_2Cl_2:2-propanol = 1:1) and then filtered through 0.20 μm membrane filter to afford 15,16-*cis*-diol **1a** (4.5 mg, quant.) as a white solid. IR (KBr) ν_{max} 3729, 1516 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ1.07 (3H, s, C*H*$_3$), 1.23 (1H, m, C*H*), 1.45-1.54 (2H, m, C*H* x2), 1.77-1.94 (2H, m, C*H* x2), 2.10-2.17 (2H, m, C*H* x2), 2.30 (1H, m, C*H*), 2.68 (1H, m, C*H*), 3.27 (1H, m, C*H*), 4.01 (1H, d, *J* = 8

Hz, C*H*OH), 4.07 (1H, d, *J* = 6.5 Hz, C*H*OH), 4.20 (1H, dd, *J* = 8, 6.5 Hz, CH_3CHOHC*H*OH), 6.50 (1H, s, aryl), 6.73 (1H, s, aryl). ^{13}C NMR (100 MHz, acetone-d_6) δ 19.4, 23.5, 26.5, 29.3, 29.4, 38.9, 46.5, 47.2, 69.6, 78.6, 79.7, 82.0, 113.1, 116.1, 128.4, 133.9, 143.5, 143.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1458. mp: 129-131 °C. $[\alpha]_D^{29}$ +52.4 (*c* 0.23, MeOH) [lit.[7] $[\alpha]_D^{20}$ +61.0 (*c* 0.36, MeOH)].

*15,16-cis-Diol **1b***. To a solution of **19b** (19.5 mg, 0.0378 mmol) in EtOAc (3.8 mL) was added Pd/$BaSO_4$ (5%, 38.2mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 8 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (CH_2Cl_2: 2-propanol = 1:1) and then filtered through 0.20 μm membrane filter to afford 15,16-*cis*-diol **1b** (14.3 mg, quant.) as a white solid. IR (KBr) ν_{max} 3437, 1637 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6) δ 1.06 (3H, s, C*H*$_3$), 1.19-1.52 (5H, m, C*H* x5), 1.66 (1H, m, C*H*), 2.13 (1H, m, C*H*), 2.44 (1H, t, *J* = 11 Hz, C*H*), 2.56-2.73 (2H, m, C*H* x2), 3.91 (1H, d, *J* = 6 Hz, C*H*OH), 4.03 (1H, dd, *J* = 9, 6 Hz, CH_3CHOHC*H*OH), 4.25 (1H, d, *J* = 9 Hz, C*H*OH), 6.51 (1H, s, aryl), 6.77 (1H, s, aryl). ^{13}C NMR (100 MHz, acetone-d_6) δ 17.2, 23.5, 27.1, 30.5, 30.7, 40.3, 44.8, 45.5, 67.8, 75.1, 80.2, 86.8, 113.6, 116.1, 128.5, 132.1, 143.8, 143.9. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1466. mp: 155-157 °C. $[\alpha]_D^{31}$ +64.1 (*c* 0.72, MeOH) [lit.[7] $[\alpha]_D^{20}$ +63.3 (*c* 0.37, MeOH)].

*Triacetate **20a***. To a solution of **19a** (11.0 mg, 0.0213 mmol) in pyridine (0.5 mL) were added Ac_2O (0.1 mL) and DMAP (0.6 mg, 0.005 mmol) at room temperature. After being stirred at room temperature for 5 h, the resulting mixture was poured into 1

N HCl. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with H_2O (1x), a saturated aqueous solution of $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residual solvents were azeotropically removed with benzene, and the resulting residue was purified by silica gel open column chromatography (hexane:EtOAc = 3:2) to afford triacetate **20a** (12.4 mg, 91% yield) as a white solid. ^{1}H and ^{13}C NMR data were identical to those reported for this compound.[7] IR (KBr) ν_{max} 1748, 1508, 1234 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s, C*H*$_3$CCOH), 1.25-1.61 (5H, m, C*H* x5), 2.01 (3H, s, C*H*$_3$C=O), 2.06 (3H, s, C*H*$_3$C=O), 2.08 (3H, s, C*H*$_3$C=O), 2.09-2.25 (2H, m, C*H* x2), 2.69-2.85 (2H, m, C*H* x2), 2.91 (1H, ddd, *J* = 13, 12, 4 Hz, C*H*), 5.12 (2H, s, C*H*$_2$ of Bn), 5.13 (2H, s, C*H*$_2$ of Bn), 5.27 (1H, d, *J* = 8 Hz, C*H*OAc), 5.29 (1H, d, *J* = 6.5 Hz, C*H*OAc), 5.59 (1H, dd, *J* = 8, 6.5 Hz, C*H*$_3$CCHOAcC*H*OAc), 6.69 (1H, s, aryl), 6.90 (1H, s, aryl), 7.27-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 20.3, 20.5, 20.9, 22.6, 25.1, 28.7, 29.8, 38.7, 45.2, 46.7, 68.7, 71.3, 72.1, 77.5, 78.6, 81.0, 113.5, 115.3, 127.3, 127.4, 127.7, 128.4, 128.5, 129.5, 133.2, 137.4, 137.6, 147.0, 147.5, 168.9, 169.0, 170.1. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{38}H_{42}O_9Na$, 665.2721; found, 665.2706. mp: 60-62 °C. $[\alpha]_D^{30}$ +30.2 (*c* 0.63, $CHCl_3$) [lit.[7] $[\alpha]_D^{19}$ +23.1 (*c* 1.015, $CHCl_3$)].

*Triacetate **20b***. To a solution of **19b** (19.3 mg, 0.0373 mmol) in pyridine (0.85 mL) were added Ac_2O (0.17 mL) and DMAP (0.8 mg, 0.007 mmol) at room temperature. After being stirred at room temperature for 5 h, the resulting mixture was poured into 1 N HCl. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with H_2O (1x), a saturated aqueous solution of $NaHCO_3$ (1x) and brine (1x), dried over Na_2SO_4, and concentrated under reduced

pressure. The residual solvents were azeotropically removed with benzene, and the resulting residue was purified by silica gel open column chromatography (hexane:EtOAc = 3:2) to afford triacetate **20b** (19.8 mg, 83% yield) as a white solid. ^{1}H and ^{13}C NMR data were identical to those reported for this compound.[7] IR (KBr) ν_{max} 1742, 1508, 1239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s, C*H*$_3$CCOH), 1.19 (1H, m, C*H*), 1.32 (1H, m, C*H*), 1.49 (1H, ddd, *J* = 15, 14.5, 3.5 Hz, C*H*), 1.65 (1H, br t, *J* = 12 Hz, C*H*), 1.72 (1H, dt, *J* = 14.5, 3 Hz), 2.00 (1H, br d, *J* = 12.5 Hz, C*H*), 2.06 (3H, s, C*H*$_3$C=O), 2.08 (3H, s, C*H*$_3$C=O), 2.09 (3H, s, C*H*$_3$C=O), 2.17 (1H, m, C*H*), 2.58 (1H, td, *J* = 11.5, 3 Hz, C*H*), 2.69-2.77 (2H, m, C*H* x2), 5.11 (2H, s, C*H*$_2$ of Bn), 5.12 (2H, s, C*H*$_2$ of Bn), 5.36 (1H, dd, *J* = 9, 5.5 Hz, CH_3CCHOAcC*H*OAc), 5.49 (1H, d, *J* = 5.5 Hz, C*H*OAc), 5.60 (1H, d, *J* = 9 Hz, C*H*OAc), 6.65 (1H, s, aryl), 6.85 (1H, s, aryl), 7.26-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 20.5, 20.6, 20.9, 22.0, 26.1, 30.1, 30.4, 39.3, 43.5, 44.4, 69.0, 71.3, 72.0, 73.1, 80.6, 84.5, 114.0, 115.3, 127.3, 127.4, 127.7, 127.8, 128.4, 129.4, 131.7, 137.4, 137.5, 147.0, 147.5, 168.6, 169.9, 170.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{38}H_{42}O_9Na$, 665.2721; found, 665.2707. mp: 120-121 °C. $[\alpha]_D^{29}$ +27.9 (*c* 1.01, $CHCl_3$) [lit.[7] $[\alpha]_D^{19}$ +27.0 (*c* 1.065, $CHCl_3$)].

*Epoxide **21***. To a solution of **18** (14.1 mg, 0.0292 mmol) in dry benzene (0.70 mL) were added $VO(acac)_2$ (2.2 mg, 0.0083 mmol) and TBHP (1.98 M solution in toluene, 0.02 mL, 0.04 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel open column chromatography (hexane:EtOAc = 1:1) to afford epoxide **21**

(13.1 mg, 90% yield) as a white powder. Relative stereochemistry of **21** was determined by NOESY correlations of the corresponding diol **22**. IR (KBr) ν_{max} 3465, 1507, 1274, 1244, 1217, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, s, C*H*$_3$), 1.25 (1H, ddd, *J* = 26, 14, 3 Hz, $CH_3CCH_AH_BCH_AH_B$), 1.48 (1H, ddd, *J* = 24, 12, 6.5 Hz, $COHCHCH_AH_B$), 1.55-1.71 (2H, m, $CH_3CCH_AH_B$, COHC*H*), 1.76 (1H, dt, *J* = 14, 3 Hz, $CH_3CCH_AH_B$), 2.15 (1H, ddd, *J* = 14, 7, 4 Hz, $CH_3CCH_AH_BCH_AH_B$), 2.34-2.46 (2H, m, $COHCHCH_AH_B$, COHCHCH), 2.74-2.88 (2H, m, $COHCHCH_AH_BCH_2$), 3.63 (2H, br s, CHOHC*H*C*H*), 3.84 (1H, br s, C*H*OH), 5.12 (4H, s, C*H*$_2$ of Bn), 6.70 (1H, s, aryl H-4), 6.91 (1H, s, aryl H-1), 7.27-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 22.9, 26.4, 29.7, 30.2, 39.6, 42.0, 56.3, 61.5, 64.0, 71.3, 72.1, 77.6, 79.3, 114.1, 115.3, 127.3, 127.4, 127.7, 128.43, 128.44, 130.3, 131.8, 137.4, 137.6, 147.0, 147.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_5Na$, 521.2298; found, 521.2293. mp: 44-46 °C. $[\alpha]_D^{29}$ +53.0 (*c* 0.66, $CHCl_3$).

*Diol **22***. This reaction was carried out according to the reported procedure with slight modification.[22] To a solution of **21** (24.0 mg, 0.0482 mmol) in DMF (1.2 mL) were added H_2O (0.27 mL) and PhCOONa (36.8 mg, 0.255 mmol) at room temperature. The reaction mixture was stirred at room temperature for 35 min, and then heated to 150 °C. After being stirred at 150 °C for 3 days, the reaction mixture was cooled to room temperature. The reaction was diluted with H_2O. The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel flash column chromatography (hexane:EtOAc = 1:1) to afford diol **22** (19.7 mg, 79% yield) as a white solid. Relative stereochemistry of **22** was determined by NOESY correlations (Figure 5). IR (KBr) ν_{max} 3356, 1507, 1117,

1019 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ1.12 (3H, s, C*H*$_3$), 1.30 (1H, m, $CH_3CCH_2CH_AH_B$), 1.41 (1H, ddd, *J* = 24, 11.5, 6 Hz, $COHCHCH_AH_B$), 1.52-1.61 (3H, m, COHC*H*, CH_3CCH_2), 2.06-2.20 (2H, m, $COHCHCH_AH_B$, $CH_3CCH_2CH_AH_B$), 2.52 (1H, dt, *J* = 12, 2.5 Hz, COHCHC*H*), 2.66-2.80 (2H, m, $COHCHCH_AH_BCH_2$), 4.02 (1H, dd, *J* = 8.5, 3 Hz, $CH_3CCHOHCHOH$), 4.13 (1H, d, *J* = 8.5 Hz, CH_3CCHOH), 4.35 (1H, d, *J* = 3 Hz, $CH_3CCHOHCHOHCHOH$), 5.10 (4H, s, CH_2 of Bn), 6.66 (1H, s, aryl H-4), 6.88 (1H, s, aryl H-1), 7.27-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 23.0, 26.4, 28.8, 30.2, 39.8, 44.0, 47.2, 71.3, 72.1, 77.1, 78.1, 79.5, 79.8, 114.1, 115.3, 127.3, 127.5, 127.7, 127.8, 128.4, 129.7, 132.3, 137.4, 137.6, 147.0, 147.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{36}O_6Na$, 539.2404; found, 539.2425. mp: 162-164 °C. $[\alpha]_D^{30}$ +49.1 (*c* 0.58, MeOH).

15,16-trans-diol ***1c***. To a solution of **22** (10.6 mg, 0.0205 mmol) in EtOAc (1.0 mL) was added $Pd/BaSO_4$ (5%, 9.5 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 2 days. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (1.0 mL) and then $Pd/BaSO_4$ (5%, 9.5 mg) was added at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 7.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (EtOAc) and then filtered through 0.20 μm membrane filter. The residue was purified by Chromatorex DIOL silica gel open column chromatography (EtOAc) to afford 15,16-*trans*-diol **1c** (5.3 mg, 77%) as a white solid. IR (KBr) ν_{max} 3389, 1519, 1108, 1090 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ1.09

(3H, s, C*H*$_3$), 1.24 (1H, m, $CH_3CCH_AH_BCH_AH_B$), 1.38-1.56 (3H, m, COHC*H*CH_AH_B, $CH_3CCH_AH_B$), 1.66 (1H, td, *J* = 14, 3.5 Hz, $CH_3CCH_AH_B$), 2.10-2.22 (2H, m, $CH_3CCH_AH_BCH_AH_B$, COHCHCH_AH_B), 2.48 (1H, td, *J* = 11.5, 3 Hz, COHCHC*H*), 2.54-2.70 (2H, m, COHCHC$H_AH_BCH_2$), 3.89 (1H, dd, *J* = 8, 3 Hz, $CH_3CCHOHCHOH$), 4.06 (1H, d, *J* = 8 Hz, CH_3CCHOH), 4.30 (1H, d, *J* = 3 Hz, COHC*H*OH), 6.49 (1H, s, aryl H-4), 6.77 (1H, s, aryl H-1). ^{13}C NMR (100 MHz, acetone-d_6) δ 18.0, 23.9, 27.7, 30.9, 40.6, 45.3, 47.9, 77.7, 79.0, 79.8, 80.3, 113.8, 116.1, 128.4, 132.1, 143.9, 144.0 (one sp^3 carbon is missing due to overlap with acetone-d_6). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1485. mp: 142-145 °C. $[\alpha]_D^{25}$ +49.1 (*c* 0.27, MeOH).

*Dihydroxylation of **14**.* To a solution of **14** (49.8 mg, 0.104 mmol) in acetone (3.5 mL) and *t*-BuOH (35 μL) were added OsO_4 (4% aqueous solution, w/v, 66 μL, 0.010 mmol) and NMO (22.8 mg, 0.195 mmol). After being stirred at room temperature for 5.5 h, to the resulting mixture was added NMO (22.5 mg, 0.192 mmol) at room temperature. After being stirred at room temperature for 16 h, the reaction was quenched with a saturated aqueous solution of $NaHSO_3$. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel flash column chromatography [$(CH_2Cl)_2$:MeCN = 2:1] to afford hydroxy ketone **23** (26.5 mg, 50% yield) as a white solid and diol **24** (14.5 mg, 27% yield) as a pale-yellow powder. Relative stereochemistry of diol **24** was determined by NOESY correlations (Figure 6). Stereochemistry of C7 in ketone **23** was determined to be *S* based on the result of the reduction of **23** with $NaBH_4$ in EtOH/THF to afford 6,7-*trans*-diol **25** and 6,7-*cis*-diol **24**. **23**: IR (KBr) ν_{max} 3466, 1660, 1594, 1015 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 1.01 (3H, s, C*H*$_3$), 1.40 (1H, m, CHOHC*H*$_A$H$_B$), 1.66 (1H, ddd, *J* = 15.5, 9, 7 Hz, CHOHCH$_A$H$_B$C*H*$_A$H$_B$), 1.99 (1H, m, CHOHCH$_A$*H*$_B$), 2.03 (1H, dd, *J* = 10.5, 1.5 Hz, COHC*H*), 2.43 (1H, ddd, *J* = 15.5, 12, 3.5 Hz, CHOHCH$_A$H$_B$CH$_A$*H*$_B$), 3.95 (1H, br d, *J* = 10.5 Hz, CH=CHC*H*), 4.11 (1H, dd, *J* = 9, 8 Hz, CH$_3$CC*H*OH), 4.51 (1H, d, *J* = 1.5 Hz, C=OC*H*OH), 5.16 (2H, s, C*H*$_2$ of Bn), 5.26 (1H, d, *J* = 12 Hz, C*H*$_A$H$_B$ of Bn), 5.30 (1H, d, *J* = 12 Hz, CH$_A$*H*$_B$ of Bn), 5.80 (1H, dd, *J* = 10, 3 Hz, C*H*=CHCH), 6.26 (1H, br d, *J* = 10 Hz, CH=C*H*CH), 7.21 (1H, s, aryl H-1), 7.26-7.52 (10H, m, Ph of Bn), 7.62 (1H, s, aryl H-4). ^{13}C NMR (100 MHz, CD_3OD) δ 19.9, 30.9, 32.0, 35.2, 52.4, 70.7, 72.0, 72.1, 78.9, 80.9, 111.3, 114.5, 124.8, 126.3, 128.6, 128.7, 128.9, 129.1, 129.5, 129.6, 132.6, 138.1, 138.4, 142.9, 148.6, 155.4, 197.0 (one sp^3 carbon is missing due to overlap with CD_3OD). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{32}O_6Na$, 535.2091; found, 535.2106. mp: 180-183 °C. $[\alpha]_D^{30}$ +24.0 (*c* 0.15, MeOH). **24**: IR (KBr) ν_{max} 3396, 1509, 1262, 1019 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 1.03 (3H, s, C*H*$_3$), 1.39 (1H, ddd, *J* = 21.5, 11.5, 8.5 Hz, CHOHC*H*$_A$H$_B$), 1.55 (1H, ddd, *J* = 15.5, 8.5, 8.5 Hz, CHOHCH$_A$H$_B$C*H*$_A$H$_B$), 1.75 (1H, d, *J* = 11.5 Hz, COHC*H*), 1.95 (1H, m, CHOHCH$_A$*H*$_B$), 2.46 (1H, ddd, *J* = 15.5, 11.5, 2.5 Hz, CHOHCH$_A$H$_B$CH$_A$*H*$_B$), 3.71 (1H, br d, *J* = 11.5 Hz, CH=CHC*H*), 4.07 (1H, dd, *J* = 8.5, 8.5 Hz, CH$_3$CC*H*OH), 4.49 (1H, d, *J* = 3.5 Hz, CHC*H*OH), 4.55 (1H, d, *J* = 3.5 Hz, CHCHOHC*H*OH), 5.10 (2H, s, C*H*$_2$ of Bn), 5.13 (2H, s, C*H*$_2$ of Bn), 5.64 (1H, dd, *J* = 10.5, 2.5 Hz, C*H*=CHCH), 6.17 (1H, d, *J* = 10.5 Hz, CH=C*H*CH), 7.03 (1H, s, aryl H-1), 7.26-7.49 (11H, m, aryl H-4, Ph of Bn). ^{13}C NMR (100 MHz, CD_3OD) δ 20.3, 31.18, 31.23, 35.5, 46.1, 52.5, 67.2, 72.5, 72.7, 79.2, 81.3, 113.4, 116.2, 128.7, 128.8, 128.9, 129.4, 131.4, 132.3, 133.0, 139.0, 148.8, 149.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_6Na$, 537.2248; found, 537.2257. mp: 95-98 °C. $[\alpha]_D^{30}$ +66.5 (*c*

0.26, MeOH).

*Reduction of **23***. To a solution of **23** (21.1 mg, 0.0421 mmol) in EtOH/dry THF (4.0 mL, 1:1) was added $NaBH_4$ (10.1 mg, 0.267 mmol) at room temperature. After being stirred at room temperature for 25 min, to the resulting mixture was added $NaBH_4$ (10.7 mg, 0.283 mmol) at room temperature. After being stirred at room temperature for 10 min, the resulting mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel flash column chromatography (CH_2Cl_2:EtOAc = 1:1) to afford major product **24** (13.5 mg, 64% yield) as a pale-yellow powder and minor product **25** (7.5 mg, 35% yield) as a pale yellow solid. **25**: IR (KBr) ν_{max} 3376, 1510, 1016 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.06 (3H, s, C*H*$_3$), 1.39 (1H, m, CHOHC*H*$_A$H$_B$), 1.55 (1H, m, CHOHCH$_A$H$_B$C*H*$_A$H$_B$), 1.96 (1H, m, CHOHCH$_A$*H*$_B$), 2.06 (1H, d, J = 11.5 Hz, COHC*H*), 2.38 (1H, ddd, J = 13, 11, 2.5 Hz, CHOHCH$_A$H$_B$CH$_A$*H*$_B$), 3.58 (1H, br d, J = 11.5 Hz, CH=CHC*H*), 4.10 (1H, t, J = 8.5 Hz, CH$_3$CC*H*OH), 4.40 (2H, br s, CHC*H*OHC*H*OH), 5.13 (2H, s, C*H*$_2$ of Bn), 5.17 (2H, s, C*H*$_2$ of Bn), 5.66 (1H, dd, J = 10.5, 2.5 Hz, CH=C*H*CH), 6.20 (1H, d, J = 10.5 Hz, C*H*=CHCH), 7.05 (1H, s, aryl H-4), 7.10 (1H, s, aryl H-1), 7.26-7.49 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, CD_3OD) δ 20.2, 31.2, 31.6, 35.2, 41.5, 52.9, 69.1, 72.4, 72.5, 74.0, 79.2, 81.5, 113.2, 119.2, 128.4, 128.7, 128.8, 129.4, 130.3, 131.7, 133.8, 138.9, 148.7, 149.9. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_6Na$, 537.2248; found, 537.2236. mp: 87-89 °C. $[\alpha]_D^{30}$ +114 (*c* 0.29, MeOH).

*6,7-cis-Diol **2a***. To a solution of **24** (10.3 mg, 0.0200 mmol) in EtOAc (1.0 mL) was added Pd/$BaSO_4$ (5%, 21.5 mg) at room temperature. After being stirred under

atmosphere of hydrogen (1 atm) at room temperature for 2 days, to the resulting mixture was added Pd/$BaSO_4$ (5%, 21.0 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 1 days. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (1.0 mL) and then Pd/$BaSO_4$ (5%, 20.2 mg) was added at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 2 days. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by DIOL preparative TLC (EtOAc) and then filtered through 0.20 μm membrane filter to afford *6,7-cis-diol* **2a** (2.6 mg, 39%) as a white solid. IR (KBr) ν_{max} 3375, 1520, 1085 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 1.00 (3H, s, CH_3), 1.21-1.34 (2H, m, C*H* x2), 1.43 (1H, ddd, *J* = 14.5, 13.5, 3.5 Hz, C*H*), 1.51-1.62 (3H, m, C*H* x2, COHC*H*), 1.65 (1H, ddd, *J* = 14.5, 10, 4.5 Hz, C*H*), 2.23 (1H, dd, *J* = 13, 3.5 Hz, C*H*), 2.46 (1H, ddd, *J* = 14.5, 14.5, 13.5 Hz, CH_2), 4.21 (1H, t, *J* = 8.5 Hz, CH_3CC*H*OH), 4.40 (1H, d, *J* = 3 Hz, C*H*OH), 4.46 (1H, d, *J* = 3 Hz, C*H*OH), 6.76 (1H, s, aryl), 7.03 (1H, s, aryl) (one proton is missing due to overlap with H_2O). ^{13}C NMR (100 MHz, acetone-d_6) δ 17.0, 27.6, 31.7, 34.7, 48.3, 48.7, 67.3, 72.0, 80.4, 82.5, 112.9, 115.4, 130.5, 132.8, 144.0, 144.8 (two sp^3 carbons are missing due to overlap with acetone-d_6). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1474. mp: 165-167 °C. $[\alpha]_D^{28}$ +44.6 (*c* 0.13, MeOH).

6,7-trans-Diol ***2b***. To a solution of **25** (7.1 mg, 0.014 mmol) in EtOAc (1.0 mL) was added Pd/$BaSO_4$ (5%, 29.6 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 4 days. The

reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by DIOL preparative TLC (hexane:acetone = 1.3) and then filtered through 0.20 μm membrane filter to afford 6,7-*trans*-diol **2b** (1.3 mg, 28%) as a white solid. IR (KBr) ν_{max} 3374, 1614, 1521, 1015 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 1.03 (3H, s, CH_3), 1.30 (1H, ddd, J = 25.5, 12.5, 3.5 Hz, $CH_3CCH_AH_BCH_AH_B$), 1.45 (1H, td, J = 13.5, 3.5 Hz, $CH_3CCH_AH_B$), 1.50-1.62 (2H, m, $CHOHCH_AH_B$, $CH_3CCH_AH_B$), 1.65 (1H, ddd, J = 15, 10, 3.5 Hz, $CHOHCH_AH_BCH_AH_B$), 1.93 (1H, d, J = 12 Hz, COHC*H*), 2.23 (1H, m, $CH_3CCH_AH_BCH_AH_B$), 2.44 (1H, ddd, J = 15, 12, 6.5 Hz, $CHOHCH_AH_BCH_AH_B$), 2.75 (1H, m, COHCHC*H*), 4.23 (1H, t, J = 8.5 Hz, CH_3CCHOH), 4.32 (1H, d, J = 2.5 Hz, C*H*OH), 4.34 (1H, d, J = 2.5 Hz, C*H*OH), 6.75 (1H, s, aryl H-4), 6.80 (1H, s, aryl H-1) (one proton is missing due to overlap with acetone-d_6 residual solvent peak). ^{13}C NMR (100 MHz, acetone-d_6) δ 17.1, 27.6, 32.2, 34.3, 43.3, 49.0, 68.9, 73.5, 80.5, 82.7, 113.1, 118.5, 129.4, 133.5, 143.9, 145.4 (two sp^3 carbons are missing due to overlap with acetone-d_6). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1473. mp: 145-147 °C. $[\alpha]_D^{24}$ +12.9 (*c* 0.07, MeOH).

*Diol **26***. A solution of I_2 (33.4 mg, 0.132 mmol) and PhCOOAg (85.9 mg, 0.375 mmol) in dry benzene (5.4 mL) was stirred at room temperature for 2 h in the dark. To this solution was added a solution of **14** (31.4 mg, 0.0654 mmol) in dry benzene (5.4 mL) at room temperature via cannula. The reaction mixture was stirred at room temperature for 30 min in the dark and then heated to reflux. After being stirred at reflux for 3 h in the dark, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford crude dibenzoate, which was used for the next reaction without further

purification. The crude dibenzoate was dissolved in MeOH (3.3 mL). To this solution was added K_2CO_3 (29.5 mg, 0.213 mmol). The reaction mixture was stirred at room temperature for 1.5 h, and then diluted with EtOAc. The resulting mixture was washed with H_2O (1x). The aqueous layer was extracted with EtOAc (2x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (hexane:EtOAc = 1:2) to afford diol **26** (10.0 mg, 30% yield in 2 steps) as a pale yellow solid. Relative stereochemistry of diol **26** was determined by NOESY correlations (Figure 6). IR (KBr) ν_{max} 3356, 1509, 1266, 1098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s, C*H*$_3$), 1.45 (1H, m, C*H*), 1.73 (1H, m, C*H*), 1.93 (1H, dd, *J* = 11, 11 Hz, COHC*H*), 2.08-2.24 (2H, m, C*H* x2), 3.28 (1H, br d, *J* = 11 Hz, CH=CHC*H*), 3.96 (1H, dd, *J* = 11, 7 Hz, CHC*H*OH), 4.16 (1H, t, *J* = 7.5 Hz, CH_3CC*H*OH), 4.64 (1H, d, *J* = 7 Hz, CHCHOHC*H*OH), 5.16 (4H, s, C*H*$_2$ of Bn), 5.69 (1H, dd, *J* = 10, 2.5 Hz, C*H*=CHCH), 6.06 (1H, d, *J* = 10 Hz, CH=C*H*CH), 6.89 (1H, s, aryl H-1), 7.14 (1H, s, aryl H-4), 7.29-7.49 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 30.7, 31.1, 39.5, 45.2, 51.2, 71.3, 71.8, 79.3, 82.3, 112.1, 113.7, 127.0, 127.35, 127.41, 127.86, 127.90, 128.50, 128.54, 129.7, 130.1, 131.0, 137.1, 148.1 (two sp^3 carbons are missing due to overlap with $CDCl_3$). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_6Na$, 537.2248; found, 537.2244. mp: 84-86 °C. $[\alpha]_D^{30}$ +74.4 (*c* 0.27, MeOH).

*6,7-trans-Diol **2c**.* To a solution of **26** (11.2 mg, 0.0218 mmol) in EtOAc (1.0 mL) was added Pd/$BaSO_4$ (5%, 35.0 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 5 days. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated

under reduced pressure. The residue was purified by DIOL preparative TLC (benzene:EtOH = 8:1) and Chromatorex DIOL silica gel open column chromatography (EtOAc) and then filtered through 0.20 μm membrane filter to afford 6,7-*trans*-diol **2c** (5.0 mg, 68%) as a white solid. IR (KBr) ν_{max} 3170, 1520, 1258, 1090 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 1.03 (3H, s, CH_3), 1.22-1.45 (2H, m, $CH_3CCH_AH_BCH_AH_B$), 1.52-1.75 (4H, m, COHC*H*, $CHOHCH_AH_BCH_AH_B$, $CH_3CCH_AH_B$), 2.10-2.31 (3H, m, $CH_3CCH_AH_BCH_AH_B$, $CHOHCH_AH_BCH_AH_B$), 2.47 (1H, td, *J* = 11.5, 3 Hz, COHCHC*H*), 3.76 (1H, dd, *J* = 11, 8.5 Hz, COHCHC*H*OH), 4.26 (1H, t, *J* = 8.5 Hz, CH_3CCHOH), 4.44 (1H, d, *J* = 8.5 Hz, COHCHCHOHC*H*OH), 6.73 (1H, s, aryl H-1), 7.00 (1H, s, aryl H-4). ^{13}C NMR (100 MHz, acetone-d_6) δ 17.3, 26.5, 29.3, 31.0, 40.7, 47.7, 47.8, 76.8, 77.8, 80.8, 83.6, 112.6, 114.9, 130.7, 131.3, 144.4, 145.3 (one sp^3 carbon is missing due to overlap with acetone-d_6). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1486. mp: 156-159 °C. $[\alpha]_D^{25}$ +40.8 (*c* 0.25, MeOH).

*Alkene **27**.* This reaction was carried out according to the reported procedure.[14a] To a solution of **14** (102 mg, 0.211 mmol) in MeOH/EtOAc (5.2 mL, 1:1) was added $(Ph_3P)_3RhCl$ (38.7 mg, 0.0418 mmol) at room temperature. After being stirred under atmosphere of hydrogen (3 atm) at room temperature for 4.5 h, the resulting mixture was filtered through Florisil, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 1:2) to afford alkene **27** (84.1 mg, 82% yield) as a yellow solid. IR (KBr) ν_{max} 3435, 1509, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, s, CH_3), 1.24-1.70 (4H, m, $CHOHCH_AH_BCH_AH_B$, COHC*H*CH_AH_B), 1.99-2.20 (3H, m, $CHOHCH_AH_BCH_AH_B$, $COHCHCH_AH_B$), 2.77-2.87 (2H, m, $COHCHCH_AH_BCH_2$), 3.15 (1H, br d, *J* = 11 Hz,

CH=CHC*H*), 4.16 (1H, dd, *J* = 9, 7 Hz, C*H*OH), 5.12 (2H, s, CH_2 of Bn), 5.14 (2H, s, CH_2 of Bn), 5.68 (1H, dd, *J* = 10.5, 3 Hz, C*H*=CHCH), 6.15 (1H, dd, *J* = 10.5, 1 Hz, CH=C*H*CH), 6.72 (1H, s, aryl H-4), 6.96 (1H, s, aryl H-1), 7.27-7.48 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 21.6, 29.3, 29.7, 30.7, 40.3, 43.1, 50.6, 71.5, 72.1, 79.1, 81.7, 112.9, 115.8, 127.3, 127.4, 127.7, 127.8, 128.3, 128.4, 129.7, 130.3, 131.5, 137.5, 137.6, 147.1, 147.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{34}O_4Na$, 505.2349; found, 505.2368. mp: 61-63 °C. $[\alpha]_D^{29}$ +92.3 (*c* 0.76, $CHCl_3$).

*Diol **28***. To a solution of **27** (20.6 mg, 0.0427 mmol) in acetone (1.4 mL) and *t*-BuOH (13 μL) were added OsO_4 (4% aqueous solution, w/v, 0.30 mL, 0.047 mmol). After being stirred at room temperature for 7.5 h, to the resulting mixture was added Me_3N^+-O^- (1.5 mg, 0.020 mmol) at room temperature. After being stirred at room temperature for 40 min, to the resulting mixture was added Me_3N^+-O^- (3.1 mg, 0.041 mmol) at room temperature. After being stirred at room temperature for 25 min, to the resulting mixture was added Me_3N^+-O^- (6.4 mg, 0.085 mmol) at room temperature. After being stirred at room temperature for 40 min, to the resulting mixture was added Me_3N^+-O^- (6.8 mg, 0.091 mmol) at room temperature. After being stirred at room temperature for 25 min, the reaction was quenched with a saturated aqueous solution of $NaHSO_3$. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel flash column chromatography (hexane:EtOAc = 1:1 to 1:2) to afford diol **28** (8.9 mg, 40% yield) as a white solid. Relative stereochemistry of diol **28** was determined by NOESY correlations (Figure 7). IR (KBr) ν_{max} 3406, 1512, 1009 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 1.21-1.34 (1H, m, COHCHC$H_A$$H_B$), 1.28 (3H, s, C$H_3$), 1.48 (1H, ddd, *J* =

14.5, 10, 4.5 Hz, CHOHCH$_A$H$_B$C*H$_A$*H$_B$), 1.69 (1H, m, CHOHC*H$_A$*H$_B$, 1.94-2.09 (2H, m, CHOHCH$_A$H$_B$CH$_A$*H$_B$*, COHC*H*), 2.13-2.26 (2H, m, COHCHCH$_A$*H$_B$*, CHOHCH$_A$*H$_B$*), 2.67 (1H, br d, *J* = 12.5 Hz, COHCHC*H*), 2.70-2.77 (2H, m, COHCHCH$_A$H$_B$C*H$_2$*), 3.80 (1H, br d, *J* = 2.5 Hz, CH$_3$CC*H*OH), 4.20 (1H, t, *J* = 8.5 Hz, C*H*OHCH$_A$H$_B$), 4.51 (1H, dd, *J* = 2.5, 2.5 Hz, CH$_3$CCHOHC*H*OH), 5.06 (2H, s, C*H$_2$* of Bn), 5.07 (1H, d, *J* = 12 Hz, C*H$_A$*H$_B$ of Bn), 5.12 (1H, d, *J* = 12 Hz, CH$_A$*H$_B$* of Bn), 6.73 (1H, s, aryl H-4), 7.01 (1H, s, aryl H-1), 7.25-7.47 (10H, m, Ph of Bn). ^{13}C NMR (100 MHz, CD$_3$OD) δ 14.7, 23.5, 29.8, 29.9, 30.8, 38.8, 43.1, 53.2, 71.4, 72.4, 73.0, 73.7, 84.5, 84.6, 115.1, 116.9, 128.7, 128.79, 128.82, 129.40, 129.43, 130.4, 132.8, 139.0, 139.1, 148.4, 148.5. HRMS-ESI (*m/z*): [M+Na]$^+$ calcd for $C_{32}H_{36}O_6Na$, 539.2404; found, 539.2390. mp: 150-152 °C. $[\alpha]_D^{29}$ +44.3 (*c* 0.35, MeOH).

*11,12-cis-Diol **3***. To a solution of **28** (6.9 mg, 0.013 mmol) in EtOAc (1.0 mL) was added Pd/BaSO$_4$ (5%, 13.8 mg) at room temperature. The reaction mixture was stirred under atmosphere of hydrogen (1 atm) at room temperature for 2.5 days. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Chromatorex DIOL silica gel open column chromatography (EtOAc) and then filtered through 0.20 μm membrane filter to afford **3** (1.9 mg, 42%) as a white solid. IR (KBr) ν_{max} 3375, 1524, 1082, 1012 cm^{-1}. ^{1}H NMR (400 MHz, acetone-*d*$_6$) δ 1.17-1.35 (2H, m, COHCHC*H$_A$*H$_B$, CHOHCH$_A$H$_B$C*H$_A$*H$_B$), 1.32 (3H, s, C*H$_3$*), 1.50 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz, CHOHCH$_A$H$_B$CH$_A$*H$_B$*), 1.71 (1H, m, CHOHC*H$_A$*H$_B$), 1.97-2.27 (3H, m, COHC*H*, CHOHCH$_A$*H$_B$*, COHCHC*H$_A$*H$_B$), 2.60-2.68 (3H, m, CHOHCHOHC*H*, COHCHCH$_A$H$_B$C*H$_2$*), 3.83 (1H, d, *J* = 2.5 Hz, CH$_3$CC*H*OH), 4.29 (1H, t, *J* = 8.5 Hz, C*H*OHCH$_A$H$_B$), 4.48 (1H, br t, *J* = 2.5 Hz, CH$_3$CCHOHC*H*OH), 6.50 (1H, s, aryl H-4),

6.82 (1H, s, aryl H-1). ^{13}C NMR (100 MHz, acetone-d_6) δ 14.7, 23.3, 30.3, 38.8, 42.7, 52.8, 71.2, 73.0, 83.6, 84.3, 114.1, 116.1, 128.6, 129.6, 143.8, 144.0 (two sp^3 carbons are missing due to overlap with acetone-d_6). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found, 359.1483. mp: 164-166 °C. $[\alpha]_D^{26}$ +57.6 (*c* 0.21, MeOH).

Na^+/K^+-ATPase inhibitory assay. The inhibitory assay was performed as previous described with slight modifications.[23] In a 96-well plate, to a solution of Na^+/K^+-ATPase (0.00011 units, from porcine cerebral cortex, Sigma-Aldrich) in 20 μL of Tris-HCl buffer (50 mM Tris-HCl, 100 mM NaCl, 20 mM KCl, 5 mM $MgCl_2$, pH 7.4) was added 30 μL of a sample (**1a-c**, **2a-c**, **3** or Ouabain) solution[24] (0.12 or 12 mM DMSO solution in Tris-HCl buffer or DMSO solution in Tris-HCl buffer as a control) on ice. After pre-incubation for 5 min at 37 °C, 4 mM ATP (Oriental Yeast) in Tris-HCl buffer (10 μL) was added to the resulting mixture. The resulting mixture was incubated for 30 min at 37 °C. The reaction was quenched with 30 mM H_2SO_4 (84 μL) and cooled on ice for 5 min. To the resulting mixture was added 28 μL of Mo solution [1.75% (w/v) ammonium heptamolybdate·$4H_2O$ in 6.3 N H_2SO_4] at room temperature. After incubation for 10 min at room temperature, 28 μL of Malachite green solution [0.0035% (w/v) malachite green, 0.35% (w/v) poly(vinyl alcohol) (PVA, M_W 16,000) in water] was added to the resulting mixture. After incubation for 20 min at room temperature, absorbance at 650 nm was measured with a microplate spectrophotometer. Inhibitory activity (%) was calculated with the following formula: (absorbance of 0 μM well – each absorbance) / (absorbance of 0 μM well – absorbance of blank well) x 100.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXXX.

Spectral data for all new compounds (PDF)

X-ray crystallographic data for acetate **8** (CIF)

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Notes

The authors declare no competing financial interest.

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