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Total syntheses of four possible stereoisomers of resolvin E3

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ABSTRACT

Resolvin E3, 17,18-dihydroxy-5*Z*,8*Z*,11*Z*,13*E*,15*E*-eicosapentaenoic acid, is a potent anti-inflammatory lipid mediator. To determine the stereochemistries of the C17- and C18-hydroxy groups of resolvin E3 and to supply a sufficient amount of material for future biological studies, we developed a highly convergent and practical route to its four possible stereoisomers. The key reactions employed here were the Horner–Wadsworth–Emmons coupling, the two copper(I)-mediated reactions between the alkynes and the propargyl tosylates, and the simultaneous reduction of the three triple bonds to the three *Z*-olefins.

1. Introduction

Resolvins are a family of lipid mediators generated during the spontaneous resolution phase of acute inflammation.[1] Resolvins E1[2] and E2,[3] which were isolated from human polymorphonuclear leukocytes by Serhan, are formed by biosynthetic oxidation of eicosapentaenoic acid (EPA, Fig. 1) via a common precursor, 18-hydroxyeicosapentaenoic acid (18-HEPE). These E series resolvins exhibited potent anti-inflammatory activity in a model of murine peritonitis, and thus show promise as new therapeutics for treatment of human disease associated aberrant inflammation.[4]

Most recently, Arita and co-workers uncovered a novel array of 18-HEPE-derived metabolites from human eosinophils.[5] Among those, 17,18-dihydroxylated compound **1**, designated as resolvin E3, was found to display potent anti-inflammatory action by limiting polymorphonuclear infiltration in zymosan-induced peritonitis. The planar structure of resolvin E3 was determined by ^{1}H NMR analysis to be 17,18-dihydroxy-5*Z*,8*Z*,11*Z*,13*E*,15*E*-eicosapentaenoic acid. However, the stereochemistries of the two hydroxy groups of **1** have not been elucidated due mainly to its limited supply from the eosinophils. To unambiguously establish the absolute stereostructure of **1** and to supply a sufficient amount of material for future biological studies, we developed an efficient and practical synthetic route to all the four possible stereoisomers of **1**.[6,7] Here we report the highly convergent total syntheses of (17*R*,18*R*)-, (17*S*,18*S*)-, (17*S*,18*R*)-, and (17*R*,18*S*)-resolvin E3.

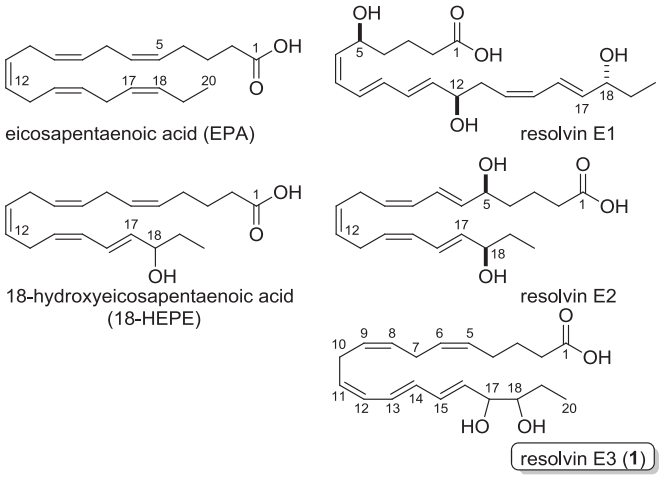

Fig. 1. Structures of EPA, 18-HEPE, and resolvins E1, E2, and E3.

2. Results and discussion

2.1. Synthetic plan of resolvin E3

The four isomers of resolvin E3 (**1a**–**d**) were retrosynthetically dissected into the four known compounds **5**, **7**, **8**, and **9** (Scheme 1). To unveil the geometrically unstable conjugated triene of **1**

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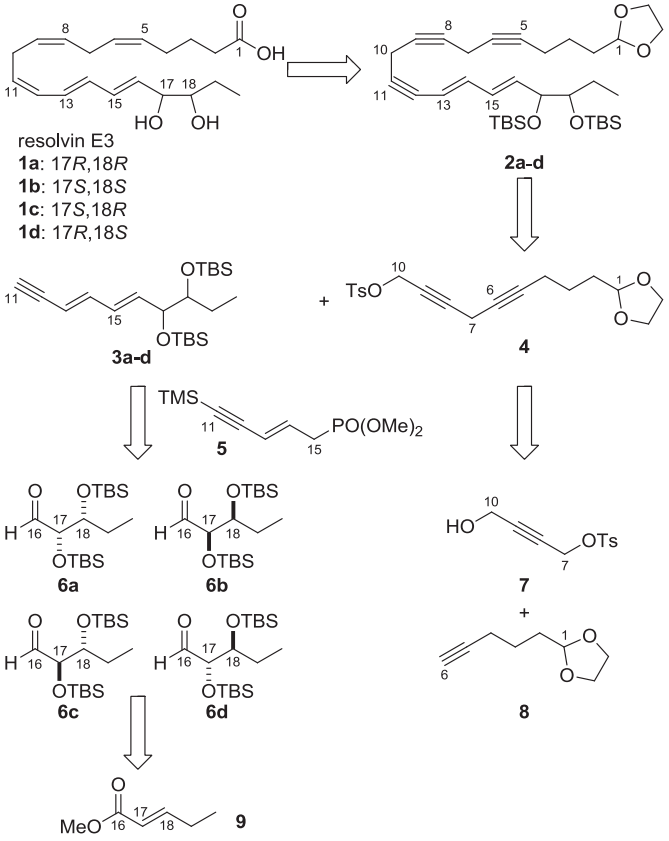
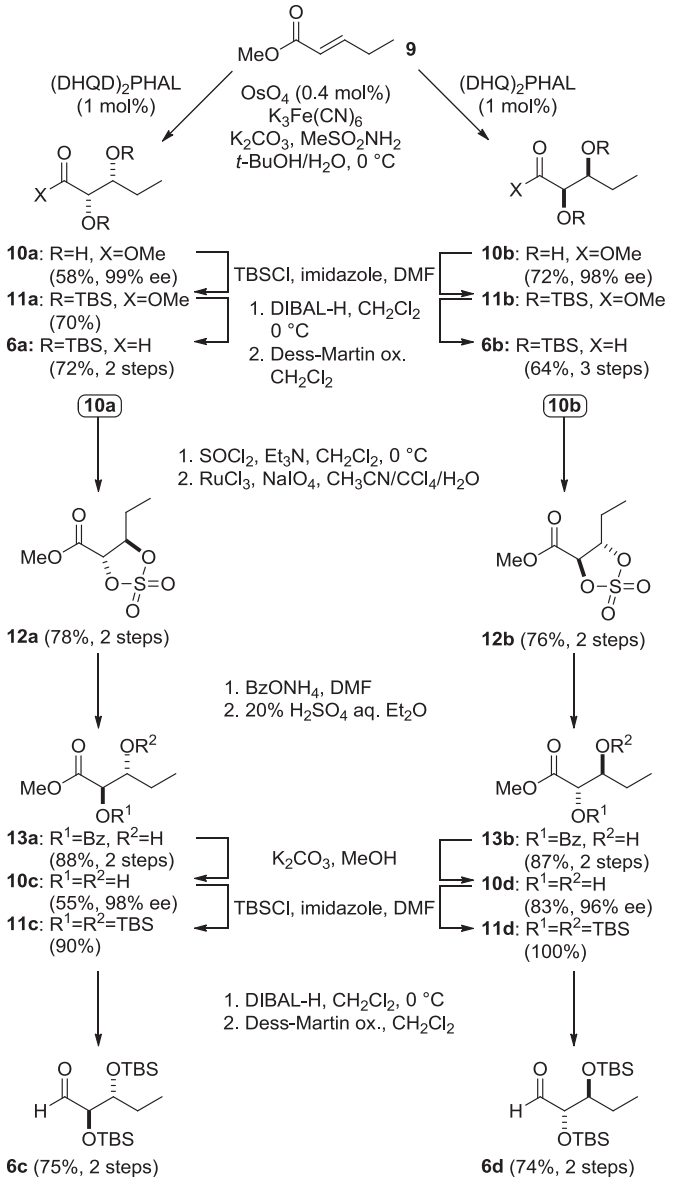
together with the 5*Z*,8*Z*-diene moiety at the last stage of the synthesis, 13*E*,15*E*-dien-5,8,11-triyne **2** was designed as the first key intermediate. In the synthetic direction, the three alkynes of **2** were to be stereoselectively reduced to the three *Z*-olefins of **1** in a single step. Compound **2** was in turn to be constructed by applying two copper(I)-mediated S_N2 reactions: C6–C7 bond formation between propargyl tosylate **7** and terminal acetylene **8**, followed by C10–C11 bond formation between **3** and **4**. Fragment **3** would be synthesized through Horner–Wadsworth–Emmons (H.W.E.) reaction of phosphonate **5** with C16–20 aldehyde **6**. We envisioned the preparation of the four chiral aldehydes **6a**–**d** from the same *E*-olefin **9** through asymmetric dihydroxylation.



Scheme 1. Retrosynthesis of resolvin E3.



Scheme 2. Syntheses of four chiral aldehydes **6a**–**d**.

2.2. Syntheses of the four chiral aldehydes

Preparation of the four enantiomerically pure aldehydes **6a**–**d** started with the Sharpless asymmetric dihydroxylation[8] of methyl 2*E*-pentenoate **9** (Scheme 2). Application of $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ to **9** as chiral ligands under the osmylation conditions provided enantiomeric diols **10a** and **10b** in enantiopure forms (vide infra).[9] After protection of diols **10a** and **10b** as their bis-TBS ethers **11a** and **11b**, respectively, reduction of their methyl esters with DIBAL-H and oxidation of the resulting primary alcohols with Dess–Martin periodinane[10] led to aldehydes **6a** and **6b**.

Alternatively, epimeric aldehydes **6c** and **6d** were synthesized from chiral diols **10a** and **10b**, respectively, via stereochemical inversion at the C17-hydroxyl groups.[9c,11] First, sulfates **12a**,**b** were prepared by treatment of the corresponding alcohols **10a**,**b** with thionyl chloride and subsequent oxidation with RuO_4.[12] Regio- and stereoselective opening of cyclic sulfates **12a**,**b** using ammonium benzoate enabled inversion of the α-position of the carbonyl group,[13] resulting in formation of benzoates **13a**,**b** after acidic hydrolysis of the sulfates. Then, methanolysis of esters **13a** and **13b** afforded diols **10c** (98% ee) and **10d** (96% ee), which were converted to enantiomeric aldehydes **6c** and **6d**, respectively, by a three-step transformation: TBS protection to **11c**,**d**, DIBAL-H reduction, and Dess–Martin oxidation.

The enantiomeric excesses of the four synthesized diols **10a**, **10b**, **10c**, and **10d** were determined to be 99%, 98%, 98%, and 96%, respectively, by the simple protocol developed by James (Fig. 2).[14] Diols **10a**–**d** were separately treated in $CDCl_3$ with 2-formylphenyl boronic acid in the presence of enantiopure (*S*)-α-methylbenzylamine, resulting in smooth formation of the corresponding diastereomeric iminoboronate esters **14a**–**d**. The imine protons (N=C*H*) and benzylic protons (NC*H*Ph) of pseudo enantiomeric **14a** and **14b**, and α-methyne protons (MeO_2CCH) of **14c** and **14d** displayed large chemical shift differences in their ^1H NMR spectra, and their integrations consequently enabled accurate quantification of the enantiomeric excess of the parent diols **10a**–**d**.

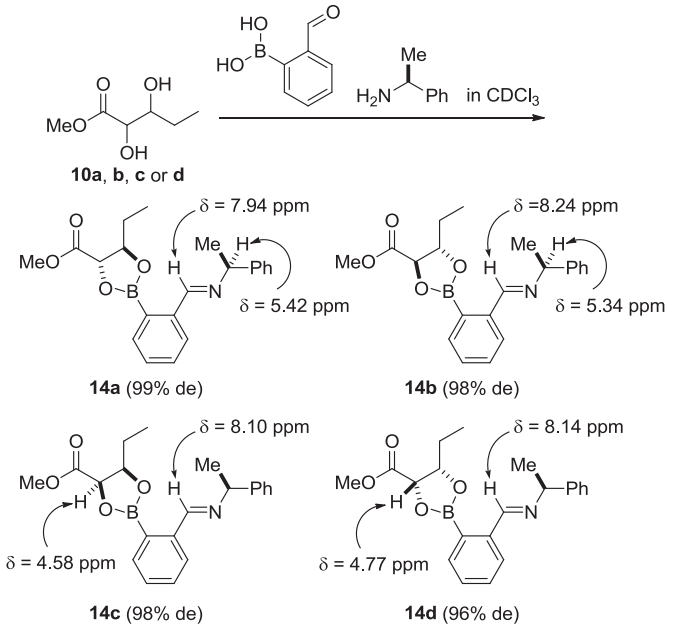
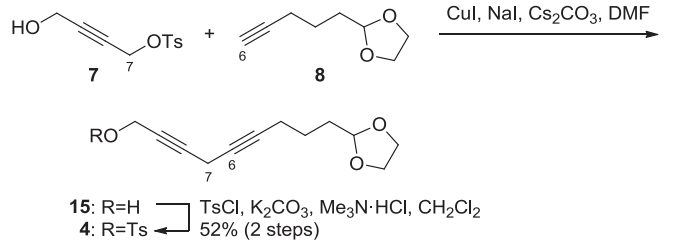


Fig. 2. Determination of enantiopurity of diols **10a**–**d**.

2.3. Synthesis of C1–10 fragment

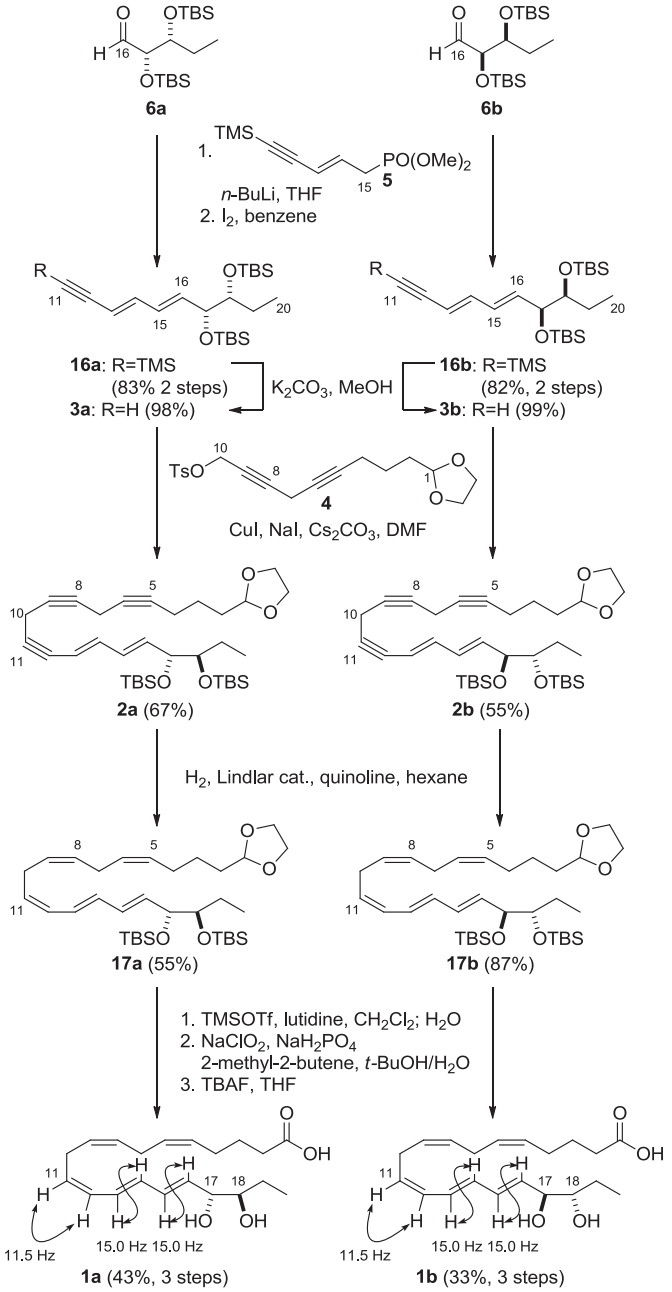
C1–10 fragment **4** was synthesized in two steps from known compounds (Scheme 3). Treatment of terminal alkyne **8**[15] with CuI in the presence of Cs_2CO_3 and NaI[16] led to the requisite acetylenic copper species, which regioselectively attacked at C7 of tosylate **7**,[17] leading to diyne **15**. To prepare for the C10-alkynylation, the remaining hydroxy group of **15** was transformed to the corresponding tosylate **4** using TsCl and K_2CO_3 in the presence of $Me_3N{\cdot}HCl$.[18] To our advantage, the undesirable nucleophilic chlorination of **4** was not observed under this Tanabe conditions.



Scheme 3. Synthesis of C1–10 fragment **4**.

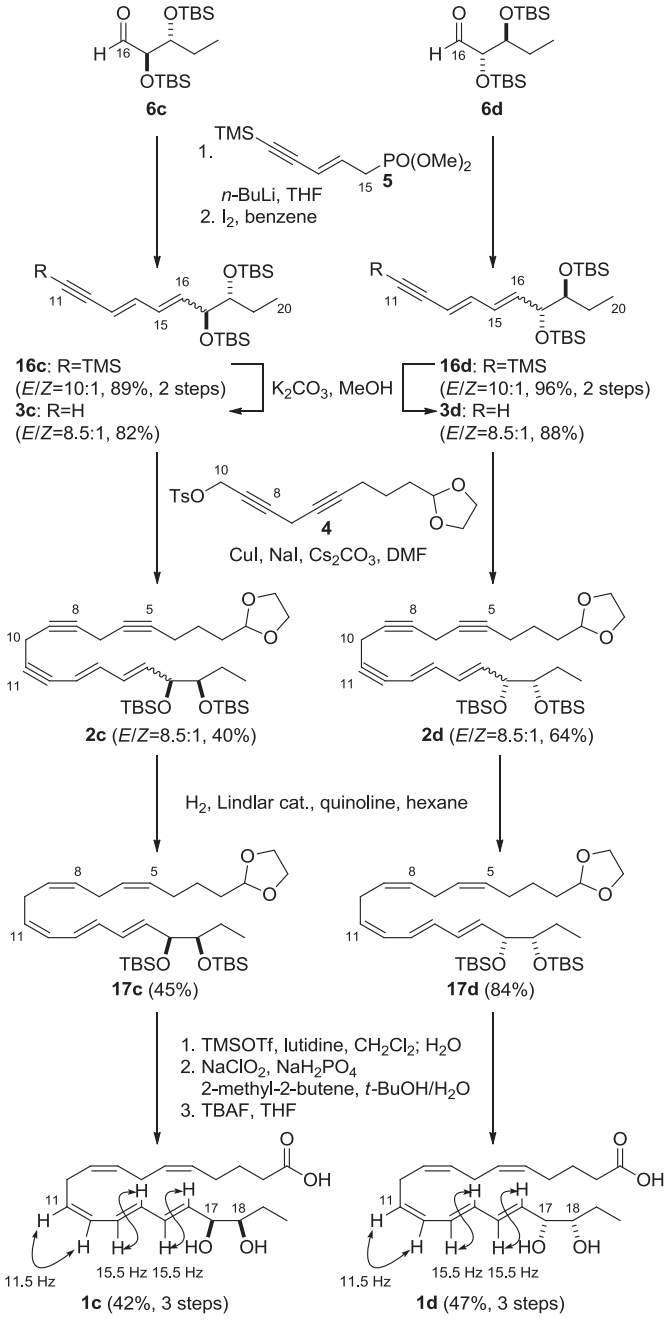
2.4. Total syntheses of the four stereoisomers of resolvin E3

Having synthesized the requisite fragments, we shifted our focus to the convergent assembly of the four isomers of resolvin E3 (**1a**–**d**). Scheme 4 illustrates the total synthesis of a pair of enantiomers **1a** and **1b** from the corresponding aldehydes **6a** and **6b**. Phosphonate **5**[19] and aldehydes **6a**,**b** were coupled by the H.W.E. reaction using *n*-BuLi as a base to generate a mixture of stereoisomers (*E*/*Z*=2.5:1).[20] The adducts were subjected to I_2-induced isomerization (*E*/*Z*=15:1), giving rise to the pure 13*E*,15*E*-dien-11-ynes **16a**,**b** after separation from the minute amount of the 15*Z*-isomer. For the last coupling reaction, the TMS groups of **16a**,**b** were removed using K_2CO_3 and MeOH to give C11–20 fragments **3a**,**b**. The reagent mixture of CuI, NaI, and Cs_2CO_3[16] effectively promoted the S_N2-type alkylation of C11–20 fragments **3a**,**b** with C1–10 propargyl tosylate **4**, leading to 13*E*,15*E*-dien-5,8,11-triynes **2a**,**b**. It is noteworthy that this coupling method using a combination of copper(I) and a weak base minimized both undesired S_N2'-type reaction of the acetylide at C8 and base-induced isomerization of the methylene-bridged 5,8,11-triyne. Chemoselective hydrogenation of the obtained triynes **2a**,**b** using Lindlar catalyst[21] in the presence of quinoline constructed the two *Z*-olefins and the unstable 11*Z*,13*E*,15*E*-triene structures of **17a**,**b** in a single step. Finally, pentaenes **17a**,**b** were converted into **1a**,**b** by following the three-step protocol previously developed for our total syntheses of the lipid mediators.[6] Selective hydrolysis of the cyclic acetals of **17a** and **17b** was attained in the presence of the TBS ethers by applying Kita's conditions,[22] providing the corresponding aldehydes. Then, $NaClO_2$ oxidation of the aldehydes into the carboxylic acids and subsequent desilylation with TBAF delivered (17*R*,18*R*)-resolvin E3 **1a** and (17*S*,18*S*)-resolvin E3 **1b**.



Scheme 4. Total synthesis of (17*R*,18*R*)- and (17*S*,18*S*)-resolvin E3.

Next, the established convergent strategy was applied to the total synthesis of (17*S*,18*R*)-resolvin E3 **1c** and (17*R*,18*S*)-resolvin E3 **1d**, the other pair of enantiomers (Scheme 5). The H.W.E. reaction of phosphonate **5** with aldehydes **6c** and **6d** provided the coupling products (*E*/*Z*=1.2:1), the newly formed olefins of which were isomerized by treatment with iodine to afford **16c** and **16d**, respectively, as a 10:1 inseparable *E*/*Z* mixture. Desilylation of **16c**,**d** was followed by the copper(I)-mediated coupling with tosylate **4**, resulting in formation of **2c**,**d** (*E*/*Z*=8.5:1). The Lindlar reduction of the three triple bonds of **2c**,**d** at the last stage successfully constructed the three *Z*-olefins, and the geometrically pure **17c**,**d** were isolated by separation of the 15*Z*-isomer. Finally, pentaenes **17c** and **17d** were transformed into **1c** and **1d**, respectively, by the three functional group manipulations. The geometries of the 11*Z*,13*E*,15*E*-triene structures of all resolvin E3s **1a**, **1b** (Scheme 4), **1c** and **1d** (Scheme 5) were confirmed based on the ^{1}H-^{1}H coupling constants.



Scheme 5. Total synthesis of (17*S*,18*R*)- and (17*R*,18*S*)-resolvin E3.

3. Conclusion

Stereoselective total syntheses of (17*R*,18*R*)-, (17*S*,18*S*)-, (17*S*,18*R*)-, and (17*R*,18*S*)-resolvin E3 (**1a**–**d**) were achieved in a highly convergent fashion from the corresponding four chiral aldehydes **6a**–**d**. The Horner–Wadsworth–Emmons coupling at C15 and the two copper(I)-mediated S_N2 reactions at C7 and C10 efficiently assembled the four simple substructures, and the late stage partial reduction greatly simplified the overall route to the target compounds. Further studies will focus on the absolute structure determination of resolvin E3 and detailed biological analysis of the natural resolvin E3 and its stereoisomers.

4. Experimental section

4.1. General

All reactions sensitive to air or moisture were carried out under argon atmosphere in dry or freshly distilled solvents under anhydrous conditions, unless otherwise noted. All other reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F_{254} pre-coated plates. Flash column chromatography was performed using 50–60 μm Silica Gel 60 (Kanto Chemical Co., Inc.). High performance liquid chromatography (HPLC) experiments were equipped with a JASCO HPLC system (pump: JASCO PU-2086 Plus x2, detector: JASCO MX-2080-32, degasser: ERC Inc. ERC3325, data analysis by JASCO ChromNAV 1.5.2.). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX-500, JNM-ECA-500 or a JNM-ECS-400 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to residual $CHCl_3$ (δ=7.26 for ^{1}H NMR and δ=77.0 for ^{13}C NMR), C_6H_6 (δ=7.16 for ^{1}H NMR), and CD_2HOD (δ=3.31 for ^{1}H NMR and δ=49.0 for ^{13}C NMR) as an internal reference. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The numbering of compounds corresponds to that of natural product. Optical rotations were recorded on a JASCO DIP-1000 Digital Polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer. High resolution mass spectra were measured on a Bruker microTOFII. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus or a Yanaco MP-J3 micro melting point apparatus, and are uncorrected.

4.1.1. Diol ***10a***. A mixture of methanesulfonamide (2.7 g, 28.4 mmol), $K_3Fe(CN)_6$ (28.1 g, 85.4 mmol), K_2CO_3 (11.8 g, 85.5 mmol), OsO_4 (1.8 mL, 0,29 mmol, 0.16 M solution in H_2O), and $(DHQD)_2PHAL$ (222 mg, 0.285 mmol) in *t*-BuOH (95 mL) and water (100 mL) was stirred for 10 min at 0 °C. A solution of ester **9** (4.0 g, 35.1 mmol) in *t*-BuOH (5 mL) was added to the mixture in one portion. The reaction mixture was stirred for 24 h at 0 °C, and saturated aqueous $Na_2S_2O_3$ (200 ml), solid NaCl, and EtOAc (100 mL) were successively added. The resultant mixture was stirred at room temperature for additional 1 h. After separation of the organic layer, the aqueous layer was extracted with EtOAc (50 mL×7). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (75 g, pentane/ether 1:1 to 1:2 to 1:4) to afford diol **10a** (3.05 g, 20.5 mmol) in 58% yield. The enantiopurity of diol **10a** was determined to be 99% ee by following the James' protocol:[14] pale yellow oil; $[\alpha]_D^{25}$ 9.3 (*c* 0.13, $CHCl_3$); IR (neat) ν 3422, 1737, 1637, 1458, 1284, 1226, 1141 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, t, *J*=7.5 Hz, $-CH_2CH_3$), 1.63 (2H, dq, *J*=7.3, 7.3 Hz, $-CHCH_2CH_3$), 2.20 (1H, d, *J*=8.7 Hz, O*H*), 3.21 (1H, d, *J*=5.5 Hz, O*H*), 3.79–3.83 (1H, m, $HOCHCH_2CH_3$), 3.81 (s, 3H, OMe), 4.12–4.14 (1H, m, COC*H*OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1, 26.8, 52.8,

72.6, 73.9, 174.1; HRMS (ESI) calcd for $C_6H_{12}NaO_4$ 171.0628 ($M+Na^+$), found 171.0628.

4.1.2. Diol ***10b***. A mixture of methansulfonamide (2.7 g, 28.4 mmol), $K_3Fe(CN)_6$ (28.1 g, 85.4 mmol), K_2CO_3 (11.8 g, 85.5 mmol), OsO_4 (1.8 mL, 0.29 mmol, 0.16 M solution in H_2O), and $(DHQ)_2PHAL$ (222 mg, 0.285 mmol) in *t*-BuOH (95 mL) and water (100 mL) was stirred for 10 min at 0 °C. A solution of ester **9** (4.0 g, 35.1 mmol) in *t*-BuOH (5 mL) was added to the mixture in one portion. The reaction mixture was stirred for 24 h at 0 °C, and saturated aqueous $Na_2S_2O_3$ (200 ml), solid NaCl, and EtOAc (100 mL) were successively added. The resultant mixture was stirred at room temperature for additional 1 h. After separation of the organic layer, the aqueous phase was extracted with EtOAc (50 mL×7). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (75 g, pentane/ether 1:1 to 1:2 to 1:4) to afford diol **10b** (3.76 g, 25.4 mmol) in 72% yield. The enantiopurity was determined to be 98% ee by following the James' protocol:[14] pale yellow oil; $[\alpha]_D^{17}$ −7.0 (*c* 0.93, $CHCl_3$); HRMS (ESI) calcd for $C_6H_{12}NaO_4$ 171.0628 ($M+Na^+$), found 171.0634; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of diol **10a**.

4.1.3. Bis-TBS ether ***11a***. TBSCl (1.14 g, 7.59 mmol) was added to a solution of diol **10a** (276 mg, 1.86 mmol) and imidazole (1.01 g, 14.9 mmol) in DMF (19 mL). After being stirred at room temperature for 13 h, the reaction mixture was cooled to 0 °C. Then, H_2O (20 mL) was added to the mixture. The resultant mixture was extracted with hexane (10 mL×3). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (25 g, hexane/EtOAc 50:1 to 15:1) to afford bis-TBS ether **11a** (489 mg, 1.30 mmol) in 70% yield: colorless oil; $[\alpha]_D^{20}$ 5.3 (*c* 1.4, $CHCl_3$); IR (neat) ν 2954, 2930, 2858, 1759, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.027 (3H, s, C*H*$_3$ of TBS), 0.033 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (3H, t, *J*=7.4 Hz, $-CH_2CH_3$), 0.90 (9H ,s, *t*-Bu of TBS), 1.38 (1H, ddq, 1H, *J*=15.1, 7.4, 7.4 Hz, $-CHCH_AH_BCH_3$), 1.75 (1H, dqd, *J*=15.1, 7.4, 6.0 Hz, $-CHCH_AH_BCH_3$), 3.69 (3H, s, OMe), 3.76 (1H, ddd, *J*=7.4, 6.0, 4.1 Hz, $-CH(TBSO)CHCH_2CH_3$), 4.19 (1H, d, *J*=4.1 Hz, COC*H*(OTBS)CH−); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −4.9, −4.5, −4.4, 10.3, 18.0, 18.3, 25.4, 25.7, 25.8, 51.4, 74.6, 75.9, 172.8; HRMS (ESI) calcd for $C_{18}H_{40}NaO_4Si_2$ 399.2357 ($M+Na^+$), found 399.2374.

4.1.4. Aldehyde ***6a***. To a solution of bis-TBS ether **11a** (478 mg, 1.27 mmol) in CH_2Cl_2 (13 mL) was added DIBAL-H (1.8 mL, 1.5 M in toluene, 2.7 mmol) dropwise at 0 °C. After being stirred for 10 min, the reaction mixture was quenched with saturated aqueous potassium sodium tartrate (10 mL) at 0 °C. Then, the resulting mixture was allowed to warm to room temperature and stirred for 30 min. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (20 mL×3). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to give crude alcohol, which was used for the next reaction without further purification.

Dess−Martin periodinane (1.15 g, 2.70 mmol) was added to a solution of the crude alcohol and $NaHCO_3$ (460 mg, 5.48 mmol) in CH_2Cl_2 (11 mL) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with H_2O (10 mL). The resultant suspension was filtered through a pad of cotton and the filtrate was extracted with CH_2Cl_2 (15 mL×3). Combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (10 g, hexane/EtOAc 30:1) to afford aldehyde **6a** (320 mg, 0.92 mmol) in 72% yield over two steps: colorless oil; $[\alpha]_D^{25}$ 58 (*c* 0.22, $CHCl_3$); IR (neat) ν 2956, 2931, 2886, 2858, 1738, 1472, 1256, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.07 (6H, s, C*H*$_3$ of TBS×2), 0.08 (3H, s, C*H*$_3$ of TBS), 0.91 (3H, m, $-CH_2CH_3$), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.36 (1H, dqd, *J*=15.1, 7.3, 7.3 Hz, $-CHCH_AH_BCH_3$), 1.76 (1H, dqd, *J*=14.7, 7.8, 5.6 Hz, $-CHCH_AH_BCH_3$), 3.79 (1H, td, *J*=7.7, 4.1 Hz, $-CHCH(OTBS)CH_2-$), 4.01 (1H, d, *J*=4.1 Hz, COC*H*(OTBS) CH−), 9.76 (1H ,s, −C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −4.60, −4.58, −4.52, 10.5, 18.0, 18.2, 25.6, 25.70, 25.72, 76.0, 79.9, 203.8; HRMS (ESI) calcd for $C_{17}H_{38}NaO_3Si_2$ 369.2252 ($M+Na^+$), found 369.2247.

4.1.5. Aldehyde ***6b***. According to the synthetic procedure of **6a**, **6b** (182 mg, 0.52 mmol) was synthesized from **10b** (120 mg, 0.81 mmol) in 64% yield over three steps by using TBSCl (440 mg, 2.90 mmol) and imidazole (440 mg, 6.47 mmol) in DMF for the first step, DIBAL-H (1.1 mL, 1.5 M in toluene, 1.65 mmol) in CH_2Cl_2 (8 mL) for the second step, Dess-Martin periodinane (420 mg, 0.99 mmol) and $NaHCO_3$ (273 mg, 3.25 mmol) in CH_2Cl_2 (7 mL) for the third step, and purification on silica gel (10 g, hexane/EtOAc 25:1): colorless oil; $[\alpha]_D^{25}$ −52 (*c* 0.12, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{38}NaO_3Si_2$ 369.2252 ($M+Na^+$), found 369.2246; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of aldehyde **6a**.

4.1.6. Sulfate ***12a***. To a solution of diol **10a** (705 mg, 4.76 mmol) and Et_3N (4.0 mL, 29 mmol) in CH_2Cl_2 (15 mL) was added $SOCl_2$ (710 μL, 9.7 mmol) dropwise at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was quenched with H_2O (30 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give sulfite, which was used for the next reaction without further purification.

$RuCl_3\cdot nH_2O$ (5.6 mg) was added to a solution of the crude sulfite in a mixture of CH_3CN (10 mL) and CCl_4 (10 mL), and the resulting mixture was cooled to 0 °C. Then, a solution of $NaIO_4$ (2.35 g, 11.0 mmol) in H_2O (20 mL) was added to the mixture. The mixture was stirred for 40 min at room temperature and additional $RuCl_3\cdot nH_2O$ (32 mg) was added. The reaction mixture was stirred for additional 30 min, and 2-propanol (5 mL) was added. After being diluted with 0.1 N HCl (100 mL), the mixture was extracted with CH_2Cl_2 (70 mL×1, 20 mL×2). Combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane/EtOAc 1:2 to 1:3) to afford sulfate **12a** (779 mg, 3.71 mmol) in 78% yield over two steps: colorless oil; $[\alpha]_D^{26}$ 46 (*c* 0.35, $CHCl_3$); IR (neat) ν 2980, 1771, 1751, 1394, 1209, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, *J*=7.3 Hz, $-CH_2CH_3$), 1.98−2.09 (2H, m, $-CHCH_2CH_3$), 3.90 (3H, s, OMe), 4.88−4.93 (2H, m, $-CH-\times2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 26.3, 53.7, 79.4, 85.1, 165.4; HRMS (ESI) calcd for $C_6H_{10}O_6SNa$ 233.0090 ($M+Na^+$), found 233.0097.

4.1.7. Sulfate ***12b***. According to the synthetic procedure of **12a**, **12b** (863 mg, 4.11 mmol) was synthesized from **10b** (796 mg, 5.38 mmol) in 76% yield over two steps by using $SOCl_2$ (800 μL, 11.0 mmol) and Et_3N (4.5 mL, 32 mmol) in CH_2Cl_2 (15 mL) for the first step, $RuCl_3\cdot nH_2O$ (56 mg) and $NaIO_4$ (2.86 g, 13.4 mmol) in a mixture of CH_3CN (10 mL), CCl_4 (10 mL), and H_2O (20 mL) for the second step, and purification on silica gel (45 g, hexane/EtOAc 1:1 to 3:1): colorless oil; $[\alpha]_D^{27}$ −42 (*c* 0.55, $CHCl_3$); HRMS (ESI) calcd for $C_6H_{10}O_6SNa$ 233.0090 ($M+Na^+$), found 233.0095; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of sulfate **12a**.

4.1.8. Benzoate ***13a***. A solution of sulfate **12a** (475 mg, 2.26 mmol) and NH_4OBz (629 mg, 4.52 mmol) in DMF (7.8 mL) was stirred at room temperature for 1 h. DMF was azeotropically removed with toluene, then the residue was diluted with Et_2O (27 mL) and 20%

aqueous H_2SO_4 (4.5 mL) at 0 °C. The mixture was stirred at room temperature for 12 h, and H_2O (30 mL) was added. The resulting mixture was extracted with EtOAc (20 mL×3), and combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (45 g, hexane/EtOAc 9:1 to 2:1). The crude product was further purified by flash column chromatography on silica gel (45 g, hexane/EtOAc 5:1 to 3:1) to afford benzoate **13a** (501 mg, 1.99 mmol) in 88% yield over two steps: colorless oil; $[\alpha]_D^{27}$ −3.9 (*c* 0.45, $CHCl_3$); IR (neat) δ 3504, 2963, 1727, 1447, 1277, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (3H, t, *J*=7.5 Hz, $-CH_2CH_3$), 1.67–1.74 (2H, m, $-CHCH_2CH_3$), 2.43 (1H, br s, O*H*), 3.79 (3H, s, OMe), 4.07–4.12 (1H, m, −CH−C*H*(OH)CH_2−), 5.29 (1H, d, *J*=4.6 Hz, COC*H*(OBz)−CH−), 7.46 (2H, dddd, *J*=8.0, 7.5, 1.7, 1.7 Hz, aromatic), 7.59 (1H, tt, *J*=8.0, 1.7 Hz, aromatic), 8.08 (2H, dd, *J*=8.0, 1.7 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9, 25.7, 52.5, 72.7, 75.5, 128.5, 129.1, 129.9, 133.5, 165.7, 169.0; HRMS (ESI) calcd for $C_{13}H_{16}O_5Na$ 275.0890 ($M+Na^+$), found 275.0901.

*4.1.9. Benzoate **13b**.* According to the synthetic procedure of **13a**, **13b** (855 mg, 3.39 mmol) was synthesized from **12b** (820 mg, 3.90 mmol) in 87% yield over two steps by using NH_4OBz (1.09 g, 7.84 mmol) in DMF (7.8 mL) for the first step, 20% aqueous H_2SO_4 (7.8 mL) in Et_2O (48 mL) for the second step, and purification on silica gel (30 g, hexane/EtOAc 7:1 to 2:1): colorless oil; $[\alpha]_D^{26}$ 3.7 (*c* 0.28, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{16}O_5Na$ 275.0890 ($M+Na^+$), found 275.0889; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of benzoate **13a**.

*4.1.10. Diol **10c**.* A mixture of benzoate **13a** (475 mg, 1.88 mmol) and K_2CO_3 (143 mg, 1.04 mmol) in MeOH (20 mL) was stirred at room temperature for 1 h. Then, brine (20 mL) and 1 M HCl (2 mL) were successively added. The resulting mixture was extracted with CH_2Cl_2 (15 mL×7), and combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (45 g, hexane/EtOAc 1:1 to 1:2) to afford diol **10c** (152 mg, 1.03 mmol) in 55% yield. The enantiopurity was determined to be 98% ee by following the James' protocol:[14] white solid; mp=50–50.5 °C (as needles recrystallized from hexane/EtOAc); $[\alpha]_D^{28}$ −25 (*c* 0.21, $CHCl_3$); IR (neat) ν 3394, 2964, 1737, 1446, 1222, 1127, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*=7.3 Hz, $-CH_2CH_3$), 1.42–1.60 (2H, m, $-CHCH_2CH_3$), 3.74–3.79 (1H, m, −CH−C*H*(OH)−CH_2−), 3.79 (s, 3H, OMe), 4.24 (1H, d, *J*=3.7 Hz, COC*H*(OH)CH−); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 24.8, 52.5, 73.8, 74.7, 173.3; HRMS (ESI) calcd for $C_6H_{12}O_4Na$ 171.0628 ($M+Na^+$), found 171.0632.

*4.1.11. Diol **10d**.* According to the synthetic procedure of **10c**, **10d** (394 mg, 2.66 mmol) was synthesized from **11b** (810 mg, 3.21 mmol) in 83% yield by using K_2CO_3 (244 mg, 1.77 mmol) in MeOH (53 mL) and purification on silica gel (45 g, hexane/EtOAc 1:1 to 1:2). The enantiopurity was determined to be 96% ee by using the James' protocol:[14] white solid; mp=46–47 °C (as needles recrystallized from hexane/EtOAc); $[\alpha]_D^{20}$ 24 (*c* 0.10, $CHCl_3$); HRMS (ESI) calcd for $C_6H_{12}O_4Na$ 171.0628 ($M+Na^+$), found 171.0625; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of diol **10c**.

*4.1.12. Bis-TBS ether **11c**.* According to the synthetic procedure of **11a**, **11c** (290 mg, 0.77 mmol) was synthesized from **10c** (127 mg, 0.86 mmol) in 90% yield by using TBSCl (516 mg, 3.43 mmol) and imidazole (469 mg, 6.90 mmol) in DMF (4.3 mL) and purification on silica gel (12 g, hexane/EtOAc 1:0 to 50:1 to 30:1 to 15:1): colorless oil; $[\alpha]_D^{26}$ 10 (*c* 0.53, $CHCl_3$); IR (neat) ν 2956, 2935, 2892, 2859, 1755, 1468, 1366, 1255, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s, C*H*$_3$ of TBS), 0.041 (3H, s, C*H*$_3$ of TBS), 0.045 (3H, s, C*H*$_3$ of TBS), 0.054 (3H, s, C*H*$_3$ of TBS), 0.86 (9H, s, *t*-Bu of TBS), 0.87 (3H, t, *J*=7.8 Hz, $-CH_2CH_3$), 0.89 (9H, s, *t*-Bu of TBS), 1.51–1.72 (2H, m, $-CHCH_2CH_3$), 3.69 (3H, s, OMe), 3.88 (1H, dt, *J*=6.0, 5.0 Hz, −CHC*H*(OTBS)CH_2−), 4.09 (1H, d, *J*=6.0 Hz, COC*H*(OTBS)CH−); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, −5.1, −4.8, −4.5, 8.3, 18.0, 18.2, 25.4, 25.6, 25.8, 51.5, 75.1, 75.2, 173.0; HRMS (ESI) calcd for $C_{18}H_{40}O_4Si_2Na$ 399.2357 ($M+Na^+$), found 399.2373.

*4.1.13. Bis-TBS ether **11d**.* According to the synthetic procedure of **11a**, **11d** (976 mg, 2.59 mmol) was synthesized from **10d** (384 mg, 2.59 mmol) in 100% yield by using TBSCl (1.56 g, 10.4 mmol) and imidazole (1.41 g, 20.7 mmol) in DMF (13 mL) and purification on silica gel (20 g, hexane/Et_2O 100:0 to 5:1): colorless oil; $[\alpha]_D^{24}$ −11 (*c* 0.57, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{40}O_4Si_2Na$ 399.2357 ($M+Na^+$), found 399.2359; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of bis-TBS ether **11c**.

*4.1.14. Aldehyde **6c**.* According to the synthetic procedure of **6a**, **6c** (105 mg, 0.303 mmol) was synthesized from **11c** (153 mg, 0.406 mmol) in 75% yield over two steps by using DIBAL−H (1.0 mL, 1.0 M in hexane, 1.0 mmol) in CH_2Cl_2 (5 mL) for the first step, Dess–Martin periodinane (269 mg, 0.634 mmol) and $NaHCO_3$ (290 mg, 3.45 mmol) in CH_2Cl_2 (5 mL) for the second step, and purification on silica gel (10 g, hexane/EtOAc 100:1 to 50:1): colorless oil; $[\alpha]_D^{25}$ 0.37 (*c* 0.31, $CHCl_3$); IR (neat) ν 2956, 2933, 2859, 1739, 1468, 1255, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s, C*H*$_3$ of TBS), 0.070 (3H, s, C*H*$_3$ of TBS), 0.074 (6H, s, C*H*$_3$ of TBS×2), 0.87 (9H, s, *t*-Bu of TBS), 0.87 (3H, t, *J*=7.8 Hz, $-CH_2CH_3$), 0.91 (9H, s, *t*-Bu of TBS), 1.53–1.66 (2H, m, $-CHCH_2CH_3$), 3.83 (1H, td, *J*=5.9, 3.7 Hz, −CHC*H*(OTBS)CH_2−), 3.89 (1H, dd, *J*=3.7, 1.8 Hz, COC*H*(OTBS)CH−), 9.60 (1H, d, *J*=1.8 Hz, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, −4.5, 9.4, 18.1, 18.3, 25.78, 25.81, 26.2, 76.5, 80.3, 203.7; HRMS (ESI) calcd for $C_{17}H_{38}O_3Si_2Na$ 369.2252 ($M+Na^+$), found 369.2265.

*4.1.15. Aldehyde **6d**.* According to the synthetic procedure of **6a**, **6d** (68 mg, 0.196 mmol) was synthesized from **11d** (100 mg, 0.265 mmol) in 74% yield over two steps by using DIBAL−H (530 μL, 1.0 M in hexane, 0.53 mmol) in CH_2Cl_2 (2.7 mL) for the first step, Dess–Martin periodinane (197 mg, 0.465 mmol) and $NaHCO_3$ (390 mg, 4.64 mmol) in CH_2Cl_2 (2.3 mL) for the second step, and purification on silica gel (12 g, hexane/EtOAc 100:0 to 99:1 to 98:2 to 97:3 to 96:4 to 95:5): colorless oil; $[\alpha]_D^{26}$ 0.39 (*c* 0.62, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{38}O_3Si_2Na$ 369.2252 ($M+Na^+$), found 369.2255; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of aldehyde **6c**.

*4.1.16. Tosylate **4**.* A solution of tosylate **7** (265 mg, 1.10 mmol) in DMF (1.5 mL) was added to a suspension of NaI (74 mg, 0.49 mmol), CuI (96 mg, 0.50 mmol), Cs_2CO_3 (164 mg, 0.50 mmol), and alkyne **8** (70 mg, 0.50 mmol) in DMF (3.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 18 h, and poured into saturated aqueous NH_4Cl (5 mL). After H_2O (15 mL) was added, the solution was extracted with EtOAc (10 mL×3). Combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (6 g, hexane/EtOAc 5:1 to 3:1 to 2:1 to 1:1) to afford propargyl alcohol **15**, which was used in the next reaction without further purification.

Tosyl chloride (181 mg, 0.95 mmol) was added to a suspension of the crude propargyl alcohol **15**, K_2CO_3 (132 mg, 0.96 mmol), and $Me_3N{\cdot}HCl$ (5.6 mg, 0.058 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 58 h, and diluted with Et_2O. The resulting solution was filtrated through a pad

of Celite with Et_2O. The filtrate was concentrated and purified by flash column chromatography on silica gel (6 g, hexane/EtOAc 4:1) to afford tosylate **4** (95 mg, 0.26 mmol) in 52% yield over two steps: yellow oil; IR (neat) ν 2952, 3884, 1365, 1180, 943 cm^{-1}; HRMS (ESI-TOF), calcd for $C_{19}H_{22}O_5SNa$ 385.1080 ($M+Na^+$), found 385.1076; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.62 (2H, m, $-CH_2CH_2CH_2-$), 1.73 (2H, m, $-CH_2CH_2CH-$), 2.18 (2H, tt, J=6.8, 2.3 Hz, $CC-CH_2CH_2-$), 2.43 (3H, s, Me of Ts), 3.01 (2H, tt, J=2.3, 2.3 Hz, $-CC-CH_2-CC-$), 3.81–3.84 (2H, m, acetal), 3.92–3.95 (2H, m, acetal), 4.67 (2H, t, J=2.3 Hz, $TsOCH_2-CC-$), 4.84 (1H, t, J=4.5 Hz, $-CH_2CH-$), 7.33 (2H, d, J=8.5 Hz, aromatic), 7.79 (2H, d, J=8.5 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8, 18.5, 21.6, 23.0, 32.8, 58.2, 64.8, 71.8, 72.7, 80.8, 84.5, 104.1, 128.1, 129.7, 133.1, 144.9.

*4.1.17. Dienyne **16a**.* *n*-BuLi (780 μL, 1.6 M in hexane, 1.25 mmol) was added dropwise to a solution of phosphonate **5** (330 mg, 1.53 mmol) in THF (7 mL) at −78 °C. The mixture was stirred at 0 °C for 10 min and cooled to −78 °C. To the mixture a solution of aldehyde **6a** (310 mg, 0.893 mmol) in THF (3 ml) was added. The reaction mixture was allowed to warm to room temperature. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (20 mL×3), and combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. Filtration of the residue through short column of silica gel with a mixture of hexane/EtOAc (15:1) afforded dienyne **16a** as a 2.5:1 *E*/*Z* mixture, which was used for the next reaction without further purification.

A mixture of the crude **16a** and I_2 (2.0 mg, 7.9 μmol) in benzene (9 mL) was stirred for 1 h at room temperature, and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3\cdot5H_2O$ (10 mL). The resulting mixture was extracted with EtOAc (10 mL×3). Combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated to give crude **16a** as a 15:1 *E*/*Z* mixture. The residue was purified by flash chromatography on silica gel (15 g, hexane/CH_2Cl_2 30:1) to afford **16a** (344 mg, 0.74 mmol) in 83% over two steps: colorless oil; $[\alpha]_D^{25}$ 86 (*c* 0.29, $CHCl_3$); IR (neat) ν 2957, 2930, 2896, 2858, 2165, 2120, 1639, 1472, 1362, 1252, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.18 (9H, s, TMS), 0.85 (3H, t, J=7.4 Hz, $-CH_2CH_3$), 0.89 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.16 (1H, dqd, J=14.2, 8.7, 7.4 Hz, $-CHCH_AH_BCH_3$), 1.58 (1H, dqd, J=14.2, 7.4, 3.6 Hz, $-CHCH_AH_BCH_3$), 3.49 (1H, ddd, J=8.7, 5.0, 3.6 Hz, $-CHCH(OTBS)CH_2-$), 4.20 (1H, dd, J=5.0, 4.6 Hz, $-CH=CHCH(OTBS)-CH-$), 5.55 (1H, d, J=15.6 Hz, $TMSCC-CH=CH-$), 5.94 (1H, dd, J=15.6, 4.6 Hz, $-CH=CHCH(OTBS)-$), 6.25 (1H, ddd, J=15.6, 11.0, 0.9 Hz, $CH=CH-CH=CHCH(OTBS)-$), 6.68 (1H, dd, J=15.6, 11.0 Hz, $TMSCC-CH=CH-$); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, −4.6, −4.3, −0.1, 10.8, 18.0, 18.2, 24.0, 25.80, 25.83, 74.9, 77.1, 96.5, 104.6, 109.7, 129.1, 136.9, 142.9; HRMS (ESI) calcd for $C_{25}H_{50}NaO_2Si_3$ 489.3011 ($M+Na^+$), found 489.2994.

*4.1.18. Dienyne **16b**.* According to the synthetic procedure of **16a**, **16b** (193 mg, 0.41 mmol) was synthesized from **6b** (172 mg, 0.50 mmol) in 82% yield over two steps by using phosphonate **5** (185 mg, 0.86 mmol) and *n*-BuLi (440 μL, 1.6 M in hexane, 0.70 mmol) in THF (2 mL) for the first step, I_2 (1.2 mg, 4.7 μmol) in benzene (5 mL) for the second step, and purification on silica gel (15 g, hexane/CH_2Cl_2 30:1): colorless oil; $[\alpha]_D^{25}$ −86 (*c* 0.43, $CHCl_3$); HRMS (ESI) calcd for $C_{25}H_{50}NaO_2Si_3$ 489.3011 ($M+Na^+$), found 489.3013; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of **16a**.

*4.1.19. Dienyne **16c**.* According to the synthetic procedure of **16a**, a crude dienyne was synthesized as a 1.2:1 *E*/*Z* mixture from **6c** (105 mg, 0.303 mmol) by using **5** (136 mg, 0.633 mmol) and *n*-BuLi (270 μL, 1.6 M in hexane, 0.43 mmol) in THF (3 mL).

The mixture was subjected to the isomerization according to the synthetic procedure of **16a** by treatment with I_2 (0.8 mg, 3 μmol) in benzene (3 mL) to give **16c** as a 10:1 *E*/*Z* mixture. The mixture was purified by a flash chromatography on silica gel (20 g, hexane/CH_2Cl_2 100:1 to 50:1 to 20:1) to afford **16c** as a 10:1 *E*/*Z* mixture (127 mg, 0.27 mmol) in 89% over two steps: colorless oil; $[\alpha]_D^{25}$ 16 (*c* 0.10, $CHCl_3$); IR (neat) ν 2958, 2929, 2891, 2858, 2161, 2122, 1472, 1252, 1108, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *E* isomer) δ −0.01 (3H, s, CH_3 of TBS), 0.00 (3H, s, CH_3 of TBS), 0.02 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.19 (9H, s, TMS), 0.86–0.89 (3H, m, $-CH_2CH_3$), 0.87 (9H, s, *t*-Bu of TBS), 0.88 (9H, s, *t*-Bu of TBS), 1.43–1.58 (2H, m, $-CHCH_2CH_3$), 3.51 (1H, dt, J=5.5, 5.5 Hz, $-CHCH(OTBS)CH_2-$), 3.98 (1H, dd, J=7.3, 5.5 Hz, $-CH=CHCH(OTBS)CH-$), 5.57 (1H, d, J=16.0 Hz, $TMSCC-CH=CH-$), 5.78 (1H, dd, J=16.0, 7.3 Hz, $-CH=CHCH(OTBS)CH-$), 6.15 (1H, dd, J=16.0, 11.0 Hz, $-C=CH-CH=CHCH(OTBS)-$), 6.66 (1H, dd, J=16.0 11.0 Hz, $-CC-CH=CH-CH=CH-$); ^{13}C NMR (125 MHz, $CDCl_3$, *E* isomer) δ −4.8, −4.5, −4.10, −4.07, 0.1, 9.1, 18.16, 18.22, 25.90, 25.94, 26.05, 75.9, 77.1, 96.9, 104.5, 110.4, 130.3, 138.4, 142.4; HRMS (ESI) calcd for $C_{25}H_{50}O_2NaSi_3$ 489.3011 ($M+Na^+$), found 489.3009.

*4.1.20. Dienyne **16d**.* According to the synthetic procedure of **16a**, a 10:1 *E*/*Z* mixture of **16d** (132 mg, 0.284 mmol) was synthesized from **6d** (102 mg, 0.295 mmol) in 96% yield over two steps by using phosphonate **5** (103 mg, 0.479 mmol) and *n*-BuLi (260 μL, 1.6 M in hexane, 0.42 mmol) in THF (3 mL) for the first step, I_2 (0.8 mg, 3 μmol) in benzene (3 mL) for the second step, and purification by a flash chromatography on silica gel (20 g, hexane/CH_2Cl_2 100:1 to 50:1 to 20:1): colorless oil; $[\alpha]_D^{24}$ −10 (*c* 0.10, $CHCl_3$); HRMS (ESI) calcd for $C_{25}H_{50}O_2NaSi_3$ 489.3011 ($M+Na^+$), found 489.3022; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of **16c**.

*4.1.21. Terminal alkyne **3a**.* A mixture of **16a** (335 mg, 0.717 mmol) and K_2CO_3 (297 mg, 2.15 mmol) in MeOH (7 ml) was stirred for 30 min at room temperature and diluted with H_2O (10 mL) and EtOAc (10 mL). After separation of the organic layer, the aqueous layer was extracted with EtOAc (10 mL×2), and combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through a pad of silica gel (5 g, hexane/EtOAc 20:1) to afford terminal alkyne **3a** (278 mg, 0.70 mmol) in 98% yield: yellow oil; $[\alpha]_D^{25}$ 109 (*c* 0.71, $CHCl_3$); IR (neat) ν 3314, 2956, 2930, 2858, 2362, 1472, 1463, 1257, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.87 (3H, t, J=7.3 Hz, $-CH_2CH_3$), 0.90 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.16 (1H, dqd, J=14.2, 9.2, 7.3 Hz, $-CHCH_AH_BCH_3$), 1.61 (1H, dqd, J=14.2, 7.3, 3.2 Hz, $-CHCH_AH_BCH_3$), 2.99 (1H, d, J=2.3 Hz, $H-CC-$), 3.50 (1H, ddd, J=9.2, 5.0, 3.2 Hz, $-CHCH(OTBS)CH_2-$), 4.22 (1H, dd, J=4.6, 3.2 Hz, $-CH=CH-CH(OTBS)CH-$), 5.51 (1H, dd, J=15.6, 2.3 Hz, $HCC-CH=CH-$), 5.97 (1H, dd, J=15.6, 4.6 Hz, $-CH=CH-CH(OTBS)-$), 6.28 (1H, ddd, J=15.6, 11.0, 1.8 Hz, $-CC-CH=CH-CH=CH-$), 6.71 (1H, dd, J=15.6, 11.0 Hz, $-CC-CH=CH-CH=CH-$),; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.84, −4.76, −4.6, −4.3, 10.8, 18.0, 18.2, 24.0, 25.80, 25.83, 74.8, 77.1, 78.9, 83.1, 108.6, 128.8, 137.1, 143.4; HRMS (ESI) calcd for $C_{22}H_{42}NaO_2Si_2$ 417.2616 ($M+Na^+$), found 417.2625.

*4.1.22. Terminal alkyne **3b**.* According to the synthetic procedure of **3a**, **3b** (154 mg, 0.390 mmol) was synthesized from **16b** (183 mg, 0.392 mmol) in 99% yield by using K_2CO_3 (168 mg, 1.22 mmol) in MeOH (5 mL) and filtration through a pad of silica gel (5 g, hexane/EtOAc 10:1): yellow oil; $[\alpha]_D^{25}$ −100 (*c* 0.69, $CHCl_3$); HRMS (ESI) calcd

for $C_{22}H_{42}NaO_2Si_2$ 417.2616 ($M+Na^+$), found 417.2599; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of **3a**.

*4.1.23. Terminal alkyne **3c**.* According to the synthetic procedure of **3a**, **3c** (90 mg, 0.23 mmol, a 8.5:1 *E*/*Z* mixture) was synthesized from **16c** (130 mg, 0.279 mmol, a 10:1 *E*/*Z* mixture) in 82% yield by using K_2CO_3 (210 mg, 1.52 mmol) in MeOH (5 mL), and purification on silica gel (20 g, hexane/EtOAc 50:1 to 20:1): yellow oil; $[\alpha]_D^{24}$ 11 (*c* 0.43, $CHCl_3$); IR (neat) ν 3313, 2956, 2932, 2887, 2858, 2098, 1469, 1362, 1254, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, *E* isomer) δ 0.00 (3H, s, C*H*$_3$ of TBS), 0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.87 (9H, s, *t*-Bu of TBS), 0.88 (3H, t, *J*=7.4 Hz, −CH_2CH_3), 0.88 (9H, s, *t*-Bu of TBS), 1.44–1.59 (2H, m, −CHC*H*$_2$CH$_3$), 3.01 (1H, d, *J*=2.3 Hz, *H*−CC−), 3.51 (1H, dt, *J*=5.2, 5.2 Hz, −CHC*H*(OTBS)CH_2−), 4.00 (1H, dd, *J*=6.9, 5.2 Hz, −CH=CH−C*H*(OTBS)CH−), 5.53 (1H, dd, *J*=16.1, 2.3 Hz, HCC−C*H*=CH−), 5.80 (1H, dd, *J*=15.5, 6.9 Hz, −CH=C*H*−CH(OTBS)−), 6.17 (1H, dd, *J*=15.5, 11.5 Hz, −CC−CH=CH−C*H*=CH−), 6.66 (1H, dd, *J*=16.1, 11.5 Hz, −CC−CH=C*H*−CH=CH−); ^{13}C NMR (125 MHz, $CDCl_3$, *E* isomer) δ −4.8, −4.5, −4.1, 9.1, 18,15, 18.23, 25.91, 25.94, 26.0, 75.9, 77.2, 79.3, 83.0, 109.3, 129.9, 138.7, 143.1; HRMS (ESI) calcd for $C_{22}H_{42}O_2NaSi_2$ 417.2616 ($M+Na^+$), found 417.2618.

*4.1.24. Terminal alkyne **3d**.* According to the synthetic procedure of **3a**, **3d** (93 mg, 0.24 mmol, a 8.5:1 *E*/*Z* mixture) was synthesized from **16d** (127 mg, 0.273 mmol, a 10:1 *E*/*Z* mixture) in 88% yield by using K_2CO_3 (193 mg, 1.44 mmol) in MeOH (5 mL) and purification on silica gel (5 g, hexane/EtOAc 50:1 to 20:1): pale yellow oil; $[\alpha]_D^{25}$ −5.6 (*c* 0.10, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{42}O_2Si_2Na$ 417.2616 ($M+Na^+$), found 417.2602; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of **3c**.

*4.1.25. Triyne **2a**.* A mixture of CuI (46 mg, 0.24 mmol), NaI (36 mg, 0.24 mmol), and Cs_2CO_3 (78 mg, 0.24 mmol) was dried in vacuo with stirring at 90 °C for 1 h. Then, a solution of **3a** (95 mg, 0.24 mmol) in DMF (3.9 mL) was added to the mixture at 0 °C. After the resulting mixture was stirred for 3 min, a solution of freshly prepared tosylate **4** (94 mg, 0.26 mmol) in DMF (0.9 ml) was added. The reaction mixture was stirred at room temperature for 19 h in the dark, and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (15 mL×1, 10 mL×2) and combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (25 g, hexane/EtOAc 20:1). The impure fractions were re-purified by flash chromatography on silica gel (8 g, hexane/EtOAc 20:1). Triyne **2a** (total 93 mg, 0.16 mmol) was obtained in 67% yield: pale yellow oil; $[\alpha]_D^{25}$ 48 (*c* 0.23, $CHCl_3$); IR (neat) ν 2955, 2928, 2857, 1471, 1462, 1256, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.06 (6H, s, C*H*$_3$ of TBS), 0.86 (3H, t, *J*=7.8 Hz, H20), 0.89 (18H, s, *t*-Bu of TBS), 1.16 (1H, dqd, *J*=16.0, 7.8, 7.8 Hz, H19a), 1.53–1.67 (3H, m, H3 and H19b), 1.75 (2H, dt, *J*=5.0, 5.0 Hz, H2), 2.22 (2H, tt, *J*=6.4, 2.3 Hz, H4), 3.13 (2H, m, H7), 3.29 (2H, d, *J*=2.3 Hz, H10), 3.48 (1H, ddd, *J*=8.2, 4.6, 3.7 Hz, H18), 3.83–3.98 (4H, m, acetal), 4.19 (1H, dd, *J*=4.6, 4.6 Hz, H17), 4.87 (1H, t, *J*=5.0 Hz, H1), 5.50 (1H, d, *J*=15.6 Hz, H13), 5.89 (1H, dd, *J*=15.1, 4.6 Hz, H16), 6.24 (1H, dd, *J*=15.1, 11.0 Hz, H15), 6.59 (1H, dd, *J*=15.6, 11.0 Hz, H14); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.7, −4.6, −4.3, 9.8, 10.6, 10.8, 18.0, 18.1, 18.6, 23.1, 24.0, 25.80, 25.83, 32.9, 64.8(×2), 74.0, 74.2, 74.9, 75.2, 77.1, 80.0, 80.2, 85.5, 104.2, 109.7, 129.1, 136.0, 141.7; HRMS (ESI) calcd for $C_{34}H_{56}NaO_4Si_2$ 607.3609 ($M+Na^+$), found 607.3591.

*4.1.26. Triyne **2b**.* According to the synthetic procedure of **2a**, **2b** (42 mg, 0.072 mmol) was synthesized from **3b** (50 mg, 0.13 mmol) in 55% yield by using tosylate **4** (55 mg, 0.15 mmol), CuI (24 mg, 0.13 mmol), NaI (19 mg, 0.13 mmol), and Cs_2CO_3 (41 mg, 0.13 mmol) in DMF (0.4 mL) and purification on silica gel (8 g, hexane/EtOAc 20:1): pale yellow oil; $[\alpha]_D^{25}$ −51 (*c* 0.25, $CHCl_3$); HRMS (ESI) calcd for $C_{34}H_{56}NaO_4Si_2$ 607.3609 ($M+Na^+$), found 607.3613; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of triyne **2a**.

*4.1.27. Triyne **2c**.* According to the synthetic procedure of **2a**, **2c** (58 mg, 0.099 mmol, a 8.5:1 *E*/*Z* mixture) was synthesized from **3c** (99 mg, 0.25 mmol, a 8.5:1 *E*/*Z* mixture) in 40% yield by using **4** (109 mg, 0.30 mmol), CuI (48 mg, 0.25 mmol), NaI (38 mg, 0.25 mmol), and Cs_2CO_3 (82 mg, 0.25 mmol) in DMF (1.3 mL) and purification on silica gel (12 g, hexane/EtOAc 1:0 to 100:1 to 50:1 to 25:1 to 10:1): yellow oil; $[\alpha]_D^{26}$ 8.9 (*c* 0.37, $CHCl_3$); IR (neat) ν 2953, 2935, 2887, 2860, 1468, 1253, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, *E* isomer) δ −0.01 (3H, s, C*H*$_3$ of TBS), 0.00 (3H, s, C*H*$_3$ of TBS), 0.02 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.86 (9H, s, *t*-Bu of TBS), 0.87 (9H, s, *t*-Bu of TBS), 0.86–0.88 (3H, m, H20), 1.45–1.67 (4H, m, H3 and H19), 1.74–1.78 (2H, m, H2), 2.23 (2H, tt, *J*=7.5, 2.3 Hz, H4), 3.14 (2H, tt, *J*=2.3, 2.3 Hz, H7), 3.30–3.32 (2H, m, H10), 3.50 (1H, dt, *J*=5.7, 5.7 Hz, H18), 3.83–3.87 (2H, m, acetal), 3.95–3.99 (3H, m, H17 and acetal), 4.87 (1H, t, *J*=4.6 Hz, H1), 5.53 (1H, br d, *J*=16.1 Hz, H13), 5.73 (1H, dd, *J*=15.5, 6.9 Hz, H16), 6.13 (1H, dd, *J*=15.5, 10.9 Hz, H15), 6.55 (1H, dd, *J*=16.1, 10.9 Hz, H14); ^{13}C NMR (100 MHz, C_6D_6, *E* isomer) δ −4.6, −4.3, −3.84, −3.76, 9.4, 9.9, 10.6, 18.43, 18.48, 18.9 , 23.7, 26.19, 26.22, 26.4, 33.4, 64.8 (two peaks), 74.3, 74.7, 75.9, 76.5, 77.4, 80.4, 80.6, 87.0, 104.5, 111.7, 131.2, 137.4, 141.2; HRMS (ESI) calcd for $C_{34}H_{56}O_4NaSi_2$ 607.3609 ($M+Na^+$), found 607.3608.

*4.1.28. Triyne **2d**.* According to the synthetic procedure of **2a**, **2d** (90 mg, 0.15 mmol, a 8.5:1 *E*/*Z* mixture) was synthesized from **3d** (93 mg, 0.24 mmol, a 8.5:1 *E*/*Z* mixture) in 64% yield by using **4** (88 mg, 0.24 mmol), CuI (53 mg, 0.28 mmol), NaI (54 mg, 0.36 mmol), and Cs_2CO_3 (91 mg, 0.28 mmol) in DMF (2 mL), and purification on silica gel (10 g, hexane/EtOAc 7:1 to 3:1 to 1:1): yellow oil; $[\alpha]_D^{25}$ −6.5 (*c* 0.13, $CHCl_3$); HRMS (ESI) calcd for $C_{34}H_{56}O_4NaSi_2$ 607.3609 ($M+Na^+$), found 607.3608; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of triyne **2c**.

*4.1.29. Pentaene **17a**.* A mixture of triyne **2a** (26 mg, 0.044 mmol), Lindlar catalyst (78 mg, 300 wt %), and quinoline (62 μL, 0.53 mmol) in hexane (4.4 mL) was stirred at room temperature under hydrogen atmosphere (1 atm) for 15 min. Additional Lindlar catalyst (100–300 wt %) was added in every 15–30 min to the reaction mixture until partially reduced products were disappeared on TLC (4000 wt % of Lindlar catalyst was added in total). The reaction mixture was filtered through a pad of Celite with EtOAc (5 mL×3). The filtrate was concentrated. The residue was purified with flash chromatography on silica gel (3 g, hexane/EtOAc 50:1) to afford pentaene **17a** (14 mg, 0.024 mmol) in 55% yield: pale yellow oil; $[\alpha]_D^{25}$ 62 (*c* 0.12, $CHCl_3$); IR (neat) ν 2954, 2926, 2857, 1471, 1463, 1256, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.047 (3H, s, C*H*$_3$ of TBS), 0.052 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.87 (3H, t, *J*=7.4 Hz, H20), 0.90 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.16–1.25 (1H, m, H19a), 1.46–1.70 (5H, m, H2, H3 and H19b), 2.12 (2H, dt, *J*=6.8, 6.8 Hz, H4), 2.82 (2H, dd, *J*=5.6, 5.6 Hz, H7), 2.97 (2H, dd, *J*=6.0, 6.0 Hz, H10), 3.49 (1H, ddd, *J*=9.6, 4.8, 4.8 Hz, H18), 3.82–3.98 (4H, m, acetal), 4.21 (1H, dd, *J*=5.2, 5.2 Hz, H17), 4.85 (1H, t, *J*=4.8 Hz, H1), 5.34–5.41 (5H, m, H5, H6, H8, H9, and H11), 5.84 (1H, dd, *J*=14.8, 4.8 Hz, H16), 6.03 (1H, dd, *J*=11.0, 11.0 Hz, H12), 6.24 (1H, dd, *J*=14.4, 11.6 Hz, H14), 6.28 (1H, ddd, *J*=14.8, 11.6, 1.2 Hz, H15), 6.43 (1H, dd, *J*=14.4, 11.0 Hz, H13); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.6, −4.3, 10.8, 18.1, 18.2, 23.96, 24.01, 25.7, 25.9, 26.2, 27.0, 33.4, 64.8 (×2), 75.1, 77.3, 104.5, 126.7, 127.7, 128.1, 128.7,

129.0, 129.6, 129.8, 130.1, 133.1, 133.7; HRMS (ESI) calcd for $C_{34}H_{62}NaO_4Si_2$ 613.4079 ($M+Na^+$), found 613.4082.

*4.1.30. Pentaene **17b**.* According to the synthetic procedure of **17a**, **17b** (20 mg, 0.034 mmol) was synthesized from **2b** (23 mg, 0.039 mmol) in 87% yield by using Lindlar catalyst (900 wt % in total) and quinoline (55 μL, 0.47 mmol) in hexane (4 mL) under H_2 atmosphere and purification on silica gel (3 g, hexane/EtOAc 50:1): pale yellow oil; $[\alpha]_D^{25}$ −78 (*c* 0.12, $CHCl_3$); HRMS (ESI) calcd for $C_{34}H_{62}NaO_4Si_2$ 613.4079 ($M+Na^+$), found 613.4098; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of pentaene **17a**.

*4.1.31. Pentaene **17c**.* According to the synthetic procedure of **17a**, **17c** (14 mg, 0.024 mmol) was synthesized from **2c** (31 mg, 0.053 mmol, a 8.5:1 *E*/*Z* mixture) in 45% yield by using Lindlar catalyst (1080 wt % in total) and quinoline (73 μL, 0.64 mmol) in hexane (5.3 mL) under H_2 atmosphere and purification on silica gel (4 g, hexane/EtOAc 1:0 to 100:1): colorless oil; $[\alpha]_D^{27}$ 2.5 (*c* 0.7, $CHCl_3$); IR (neat) ν 3013, 2943, 2862, 1464, 1254, 1105, 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, C*H*$_3$ of TBS), 0.02 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.86–0.90 (21H, m, *t*-Bu of TBS×2 and H20), 1.45–1.57 (4H, m, H3 and H19), 1.66–1.70 (2H, m, H2), 2.12 (2H, dt, *J*=6.9, 6.9 Hz, H4), 2.82 (2H, dd, *J*=5.8, 5.8 Hz, H7), 2.97 (2H, dd, *J*=5.7, 5.7 Hz, H10), 3.51 (1H, td, *J*=5.8, 5.2 Hz, H18), 3.83–3.86 (2H, m, acetal), 3.95–3.98 (2H, m, acetal), 3.99 (1H, dd, *J*=7.5, 5.2 Hz, H17), 4.86 (1H, t, *J*=4.6 Hz, H1), 5.34–5.42 (5H, m, H5, H6, H8, H9, and H11), 5.66 (1H, dd, *J*=14.3, 7.5 Hz, H16), 6.04 (1H, dd, *J*=11.5, 10.9 Hz, H12), 6.14 (2H, m, H14 and H15), 6.45 (1H, dd, *J*=14.9, 10.9 Hz, H13); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.5, −4.1, −4.0, 9.3, 18.19, 18.25, 24.0, 25.7, 25.96, 25.97, 26.02, 26.2, 27.0, 33.4, 64.8 (two peaks), 76.5, 77.4, 104.5, 127.2, 127.6, 128.1, 128.7, 128.9, 129.8, 130.0, 131.5, 132.8, 135.3; HRMS (ESI) calcd for $C_{34}H_{62}O_4Si_2Na$ 613.4079 ($M+Na^+$), found 613.4081.

*4.1.32. Pentaene **17d**.* According to the synthetic procedure of **17a**, **17d** (16 mg, 0.027 mmol) was synthesized from **2d** (19 mg, 0.032 mmol, a 8.5:1 *E*/*Z* mixture) in 84% yield by using Lindlar catalyst (450 wt % in total) and quinoline (46 μL, 0.33 mmol) in hexane (3.3 mL) under H_2 atmosphere and purification on silica gel (8 g, hexane/EtOAc 99:1 to 50:1 to 33:1 to 24:1): colorless oil; $[\alpha]_D^{25}$ −4.3 (*c* 0.11, $CHCl_3$); HRMS (ESI) calcd for $C_{34}H_{62}O_4Si_2Na$ 613.4079 ($M+Na^+$), found 613.4080; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of pentaene **17c**.

*4.1.33. (17R,18R)-Resolvin E3 (**1a**).* To a solution of pentaene **17a** (22 mg, 0.037 mmol) and 2,6-lutidine (95 μL, 0.82 mmol) in CH_2Cl_2 (1.4 mL), was added TMSOTf (100 μL, 0.55 mmol) dropwise at −20 °C. The reaction mixture was stirred for 1 h at −20 °C and then H_2O (1.4 mL) was added. After being stirred at room temperature for 1 h, the reaction mixture was extracted with CH_2Cl_2 (5 mL×3). Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude aldehyde, which was used for the next reaction without further purification.

A suspension of the crude aldehyde, $NaH_2PO_4{\cdot}2H_2O$ (56 mg, 0.31 mmol), and $NaClO_2$ (29 mg, 0.32 mmol) in a mixture of H_2O (0.5 mL), *t*-BuOH (0.5 mL), and 2-methyl-2-butene (0.5 mL) was stirred at room temperature for 1 h, and then diluted with H_2O (3 mL) and EtOAc (3 mL). The resulting mixture was extracted with EtOAc (10 mL×3) and combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash chromatography on silica gel (3 g, hexane/EtOAc/AcOH 10:1:0.05) to afford crude carboxylic acid, which was used for the next reaction without further purification.

TBAF (110 μl, 1 M in THF, 0.11 mmol) was added to a solution of the crude carboxylic acid in THF (1.2 mL). After the reaction mixture was stirred at room temperature for 2.5 h, additional TBAF (50 μl, 0.05 mmol) was added. After the reaction mixture was stirred at room temperature for 1.5 h, additional TBAF (100 μl, 0.1 mmol) was added again. After being stirred for additional 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (10 mL×4), and combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1 g, hexane/EtOAc/AcOH 1:1:0.05) to afford (17*R*,18*R*)-resolvin E3 **1a** along with a small amount of its 11*E* isomer. This mixture was further purified with HPLC (Inertsil ODS-3, CH_3CN/H_2O/AcOH 50:50:0.05, 3 mL/min, t_R=26 min) to afford *(17R,18R)-Resolvin E3 (**1a**)* (5.5 mg, 0.016 mmol) in 43% yield over three steps: clear oil; $[\alpha]_D^{25}$ 34 (*c* 0.16, MeOH); IR (neat) ν 3427, 3014, 2931, 1707, 1407, 1260, 995 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.97 (3H, t, *J*=7.5 Hz, H20), 1.36 (1H, ddq, *J*=14.0, 9.0, 7.5 Hz, H19a), 1.58 (1H, dqd, *J*=14.0, 7.5, 3.5 Hz, H19b), 1.67 (2H, tt, *J*=7.5, 7.5 Hz, H3), 2.13 (2H, td, *J*=7.5, 7.0 Hz, H4), 2.29 (2H, t, *J*=7.5 Hz, H2), 2.85 (2H, dd, *J*=6.0, 6.0 Hz, H7), 2.99 (2H, dd, *J*=6.0, 6.0 Hz, H10), 3.34 (1H, ddd, *J*=9.0, 7.0, 3.5 Hz, H18), 3.97 (1H, dd, *J*=7.0, 7.0 Hz, H17), 5.35–5.42 (5H, m, H5, H6, H8, H9, and H11), 5.74 (1H, dd, *J*=15.0, 7.0 Hz, H16), 6.04 (1H, dd, *J*=11.5, 11.5 Hz, H12), 6.24 (1H, dd, *J*=15.0, 11.0 Hz, H14), 6.37 (1H, dd, *J*=15.0, 11.0 Hz, H15), 6.58 (1H, dd, *J*=15.0, 11.5 Hz, H13); ^{13}C NMR (100 MHz, CD_3OD) δ 10.6, 26.2, 26.55, 26.59, 27.1, 27.7, 34.8, 76.6, 77.3, 128.6, 129.2, 129.66, 129.71, 129.8, 130.2, 131.2, 133.4, 133.7, 134.4, 179.5 (deduced from HMBC correlation with H2); HRMS (ESI) calcd for $C_{20}H_{30}NaO_4$ 357.2036 ($M+Na^+$), found 357.2029.

*4.1.34. (17S,18S)-Resolvin E3 (**1b**).* According to the synthetic procedure of **1a**, **1b** (3.7 mg, 0.011 mmol) was synthesized from **17b** (20 mg, 0.034 mmol) in 33% yield over three steps by using TMSOTf (90 μL, 0.5 mmol) and 2,6-lutidine (90 μL, 0.77 mmol) in CH_2Cl_2 (1 mL) and H_2O (2 mL) for the first step, $NaClO_2$ (28 mg, 0.31 mmol) and $NaH_2PO_4{\cdot}H_2O$ (53 mg, 0.30 mmol) in a mixture of H_2O (0.4 mL), *t*-BuOH (0.4 mL), and 2-methyl-2-butene (0.4 mL) for the second step, TBAF (80 μL, 1 M in THF, 0.08 mmol) in THF (1 mL) for the third step, and purification on HPLC (Inertsil ODS-3, CH_3CN/H_2O/AcOH 50:50:0.05, 3 mL/min, t_R=26 min): clear oil; $[\alpha]_D^{25}$ −33 (*c* 0.24, MeOH); HRMS (ESI) calcd for $C_{20}H_{30}NaO_4$ 357.2036 ($M+Na^+$), found 357.2048; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of (17*R*,18*R*)-resolvin E3 (**1a**).

*4.1.35. (17S,18R)-Resolvin E3 (**1c**).* According to the synthetic procedure of **1a**, **1c** (3.5 mg, 0.010 mmol) was synthesized from **17c** (14 mg, 0.024 mmol) in 44% yield over three steps by using TMSOTf (110 μL, 0.61 mmol) and 2,6-lutidine (110 μL, 0.95 mmol) in CH_2Cl_2 (3.6 mL) and H_2O (3 mL) for the first step, $NaClO_2$ (19 mg, 0.21 mmol) and $NaH_2PO_4{\cdot}H_2O$ (35 mg, 0.20 mmol) in a mixture of H_2O (1.5 mL), *t*-BuOH (1.5 mL), and 2-methyl-2-butene (1.5 mL) for the second step, TBAF (0.14 mL, 1 M in THF, 0.14 mmol) in THF (1 mL) for the third step, and purification on HPLC (Inertsil ODS-3, CH_3CN/H_2O/AcOH 50:50:0.05, 3 mL/min, t_R=24 min): colorless oil; $[\alpha]_D^{27}$ −7.5 (*c* 0.18, MeOH); IR (neat) ν 3404, 3013, 2963, 2930, 2878, 1712, 1401, 1240, 995 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.98 (3H, t, *J*=7.5 Hz, H20), 1.38 (1H, ddq, *J*=14.3, 9.2, 7.5 Hz, H19a), 1.60 (1H, dqd, *J*=14.3, 7.5, 4.3 Hz, H19b), 1.67 (2H, tt, *J*=7.5, 7.5 Hz, H3), 2.14 (2H, dt, *J*=7.5, 7.5 Hz, H4), 2.29 (2H, t, *J*=7.5 Hz, H2), 2.85 (2H, dd, *J*=5.8, 5.8 Hz, H7), 2.99 (2H, dd, *J*=6.3, 6.3 Hz, H10), 3.41 (1H, ddd, *J*=9.2, 5.2, 4.0 Hz, H18), 3.98 (1H, dd, *J*=7.5, 5.2 Hz, H17), 5.35–5.43 (5H, m, H5, H6, H8, H9, and H11), 5.81 (1H, dd, *J*=15.5, 7.5 Hz, H16), 6.04 (1H, dd, *J*=11.5, 11.5 Hz, H12), 6.25 (1H, dd, *J*=15.5, 10.9 Hz, H14), 6.36 (1H, dd, *J*=15.5, 10.9 Hz, H15), 6.58 (1H, dd, *J*=15.5, 11.5 Hz, H13); ^{13}C NMR (125 MHz, CD_3OD) δ 10.6, 26.1, 26.6, 26.7, 27.1, 27.6, 34.6, 76.5, 77.3, 128.6, 129.0, 129.6, 129.7, 129.8, 130.2, 131.1, 133.4, 133.9, 134.2, 177.8 (deduced from HMBC correlation

with H2); HRMS (ESI) calcd for $C_{20}H_{30}O_4Na$ 357.2036 ($M+Na^+$), found 357.2037.

*4.1.36. (17R,18S)-Resolvin E3 (**1d**).* According to the synthetic procedure of **1a**, **1d** (2.2 mg, 6.6 μmol) was synthesized from **17d** (8.4 mg, 0.014 mmol) in 47% yield over three steps by using TMSOTf (64 μL, 0.35 mmol) and 2,6-lutidine (61 μL, 0.52 mmol) in CH_2Cl_2 (2.1 mL) and H_2O (2 mL) for the first step, $NaClO_2$ (12 mg, 0.13 mmol) and $NaH_2PO_4 \cdot H_2O$ (20 mg, 0.11 mmol) in a mixture of H_2O (0.7 mL), *t*-BuOH (0.7 mL), and 2-methyl-2-butene (0.7 mL) for the second step, TBAF (0.10 mL, 1 M in THF, 0.10 mmol) in THF (1 mL) for the third step, and purification on HPLC (Inertsil ODS-3, CH_3CN/H_2O/AcOH 50:50:0.05, 3 mL/min, t_R=24 min): colorless oil; $[\alpha]_D^{27}$ 7.7 (*c* 0.15, MeOH); HRMS (ESI) calcd for $C_{20}H_{30}O_4Na$ 357.2036 ($M+Na^+$), found 357.2033; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of (17*S*,18*R*)-resolvin E3 (**1c**).

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Supplementary data

^1H and ^{13}C NMR spectra of all newly synthesized compound. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.045.

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