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Total synthesis of four stereoisomers of (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid and their *anti*-inflammatory activities

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ABSTRACT

The four stereoisomers of novel lipid mediator **1**, (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid, were synthesized from six simple fragments. Triyne **2** was convergently assembled through three S_N2 alkynylation reactions and one Sonogashira coupling reaction. Two of the three alkynes of **2** were hydrogenated using Lindlar catalyst, while the third alkyne was reduced through formation of the alkyne-dicobalt hexacarbonyl complex and subsequent reductive decomplexation, producing the requisite tetraene structure in a stereoselective manner. Next, a two-step functional group manipulation at C1, followed by simultaneous deprotection and epoxide formation, gave rise to the four isomers, (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**. The present work allowed determination of the absolute structure of naturally occurring **1** to be **1aa** and **1ab**, as well as biological evaluation of the two natural (**1aa**, **1ab**) and two unnatural (**1ba**, **1bb**) isomers. Intriguingly, natural **1aa** and unnatural **1ba** were found to exhibit more potent *anti*-inflammatory activities than **1ab** and **1bb**, indicating the greater importance of the stereochemistry of the C17,18-epoxide compared to that of the C12-hydroxy group.

1. Introduction

Omega-3 polyunsaturated fatty acids exhibit therapeutic effects towards various human inflammatory disorders.[1] Recently, many oxidized metabolites of eicosapentaenoic acid (EPA, Fig. 1), an omega-3 polyunsaturated fatty acid comprising 20 carbons and five *Z*-olefins, have been identified from inflamed biogenetic sources. Resolvins E1,[2] E2,[3] and E3[4] are metabolites of EPA produced by human polymorphonuclear leukocytes or eosinophils.[5] Biosynthetically, aspirin-acetylated COX (cyclooxygenase)-2 or cytochrome P450 monooxygenase first oxidize EPA into 18-hydroxy-eicosapentaenoic acid, which further undergoes oxidation to produce resolvins by the action of 5-LOX (lipoxygenase) or 12/15-LOX. Resolvins possess potent *anti*-inflammatory activity at nanomolar concentrations, suggesting that these endogenous compounds play an active role in resolving acute inflammations.[6]

Determination of the absolute structures of lipid mediators has been highly challenging due to their extremely low availability from biogenetic sources. Although the planar structures were deduced from UV spectroscopic and LC-MS/MS analyses using small amounts of material, full NMR assignments of the stereochemistries of the hydroxy groups have not generally been realized. Consequently, the extensive effort has been devoted to the total chemical construction of lipid mediators,[7,8] and the synthesis of all possible stereoisomers of these lipid mediators has enabled the NMR and HPLC analyses that led to elucidation of their absolute configurations. Accordingly, we previously reported the total synthesis of the four stereoisomers of resolvin E3[7c] and showed that two isomers are naturally occurring.

More recently, it was reported that peritoneal fluid of an EPA-supplemented murine model of acute inflammation contained the structurally distinct metabolite **1** of EPA (Fig. 1).[9] The potent *anti*-inflammatory activity of **1** was demonstrated by its inhibition of infiltration of polymorphonuclear (PMN) leukocytes in murine zymosan-induced peritonitis, and against leukotriene B_4-induced neutrophil chemotaxis and polarization. While the biosynthesis of all resolvins of the E-class involves the formation of 18-hydroxy-eicosapentaenoic acid, **1** appears to be derivatized through an alternative key intermediate produced from EPA. Specifically, the intermediacy of 17,18-epoxy-5,8,11,14-eicosatetraenoic acid was indicated by its detection in the above murine peritoneal fluid and by a separate in vitro experiment, where porcine 12-LOX transformed 17,18-epoxy-5,8,11,14-eicosatetraenoic acid into **1**. Thus,

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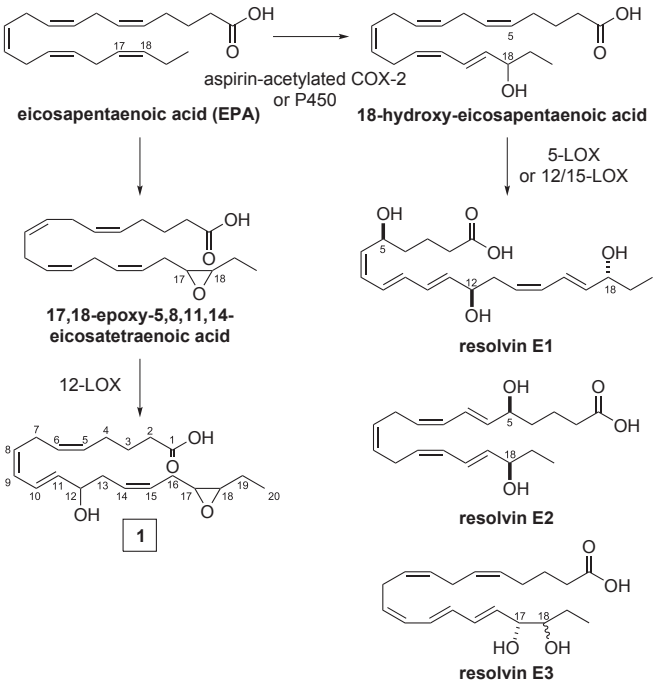


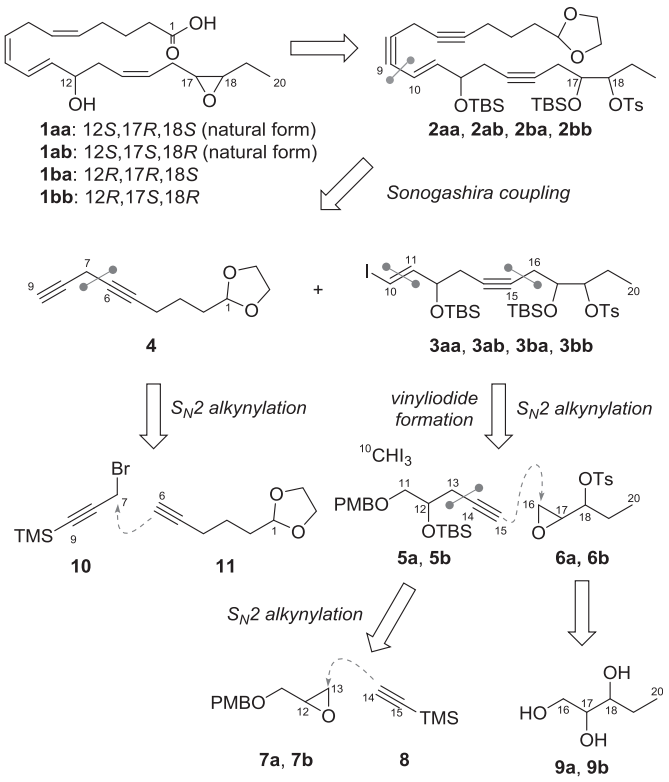
Fig. 1. Structures of EPA and its metabolites, and possible biosynthetic pathways of the metabolites.

a new endogenous *anti*-inflammatory cascade was proposed by the isolation of **1**.

UV and LC-MS/MS spectra were the only available data for natural **1** and allowed tentative assignment of its planar structure to be (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid, leaving the stereochemistry of the C12-hydroxy and C17,18-epoxide groups unassigned. We therefore embarked on establishing the absolute configuration of **1** by full synthetic construction of the four stereoisomers of **1**. Here we report details of the stereoselective total synthesis of (12*S*,17*R*,18*S*)-, (12*S*,17*S*,18*R*)-, (12*R*,17*R*,18*S*)- and (12*R*,17*S*,18*R*)-(5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa**, **1ab**, **1ba** and **1bb**). HPLC comparison analyses revealed that the EPA-derived natural **1** is **1aa** and **1ab**. Furthermore, evaluation of the *anti*-inflammatory activities of synthetic **1aa**, **1ab**, **1ba** and **1bb** demonstrated that the stereochemistry of the C17,18-epoxide has greater biological importance than that of the C12-hydroxy group.

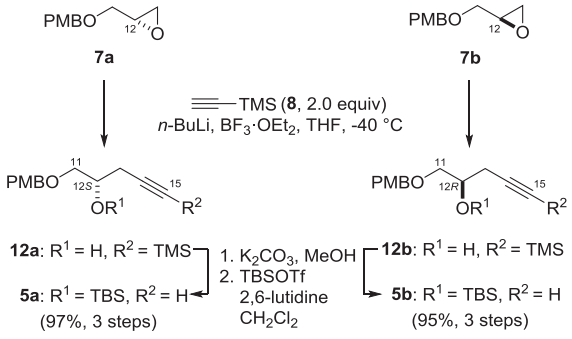
2. Results and discussion

We mapped out a convergent route to the four stereoisomers of (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa**, **1ab**, **1ba** and **1bb**, Scheme 1), and designed two chiral fragments (**7a**/**7b**, **9a**/**9b**), three achiral fragments (**8**, **10**, **11**) and iodoform for the assembly. The chemically unstable C17,18-epoxide of **1** would be constructed in the very last step of the synthesis, and the *Z*-alkenes would be generated from the corresponding internal alkynes. These retrosynthetic considerations led to intermediate **2**, which possesses a C17-hydroxy group and a C18-tosylate for epoxide formation, and three internal alkynes (C5–6, C8–9, and C14–15) as surrogates of the *Z*-alkenes. The carbon backbone of **2** would be assembled by Sonogashira coupling of C10–20 fragments **3** and the copper alkynide of C1–9 fragment **4**. Achiral **4** would be readily synthesized from **10** and **11** by applying copper-mediated S_N2-alkynylation. On the other hand, the four stereoisomers of chiral **3** (**3aa**, **3ab**, **3ba**, **3bb**) would be synthesized through S_N2-alkynylative coupling of the enantiomeric pairs of C11–15 fragment **5a**/**5b** and C16–20 fragment **6a**/**6b**, followed by vinyl iodide formation using iodoform. Compounds **5a**/**5b** would be further dissected into glycidol derivative **7a**/**7b** and TMS-acetylene **8**, while **6a**/**6b** would be simplified into triol **9a**/**9b**.



Scheme 1. Synthetic plan of the four stereoisomers of **1**.

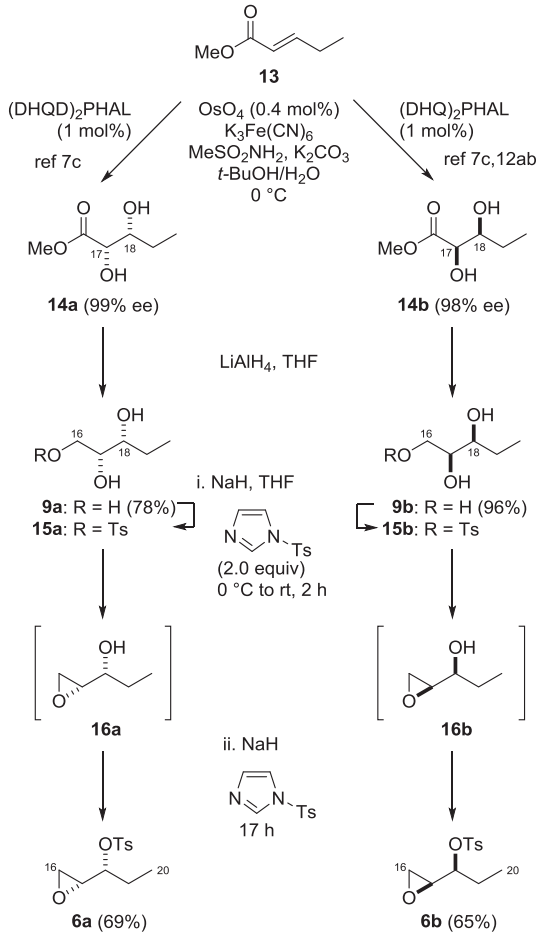
The synthesis commenced with preparation of two C11–15 fragments, **5a** and **5b** (Scheme 2). The lithium acetylide of TMS-acetylene **8** reacted with PMB-protected glycidol **7a**[10] in the presence of $BF_3 \cdot OEt_2$, leading to **12a**.[11] Removal of the C15-TMS group of the resultant **12a** was followed by TBS-protection of the C12-hydroxy group to afford (12*S*)-**5a**. The enantiomer (12*R*)-**5b** was synthesized from **7b** by employing the same three-step sequence.



Scheme 2. Synthesis of C11–15 fragments **5a** and **5b**.

C16–20 fragments **6a** and **6b**, the coupling partners of C11–15 fragments **5a** and **5b**, were synthesized from **13** (Scheme 3). Enantiomeric *syn*-diols **14a** (99% ee) and **14b** (98% ee)[7c,12] were prepared from olefin **13** by Sharpless asymmetric dihydroxylation[13] using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, respectively, as the chiral ligand. Ester **14a** was reduced with $LiAlH_4$ to provide triol **9a**,[12b] which was then converted to C16–20 fragment **6a** by treatment with NaH and tosyl imidazole.[14] Remarkably, this one-pot reaction

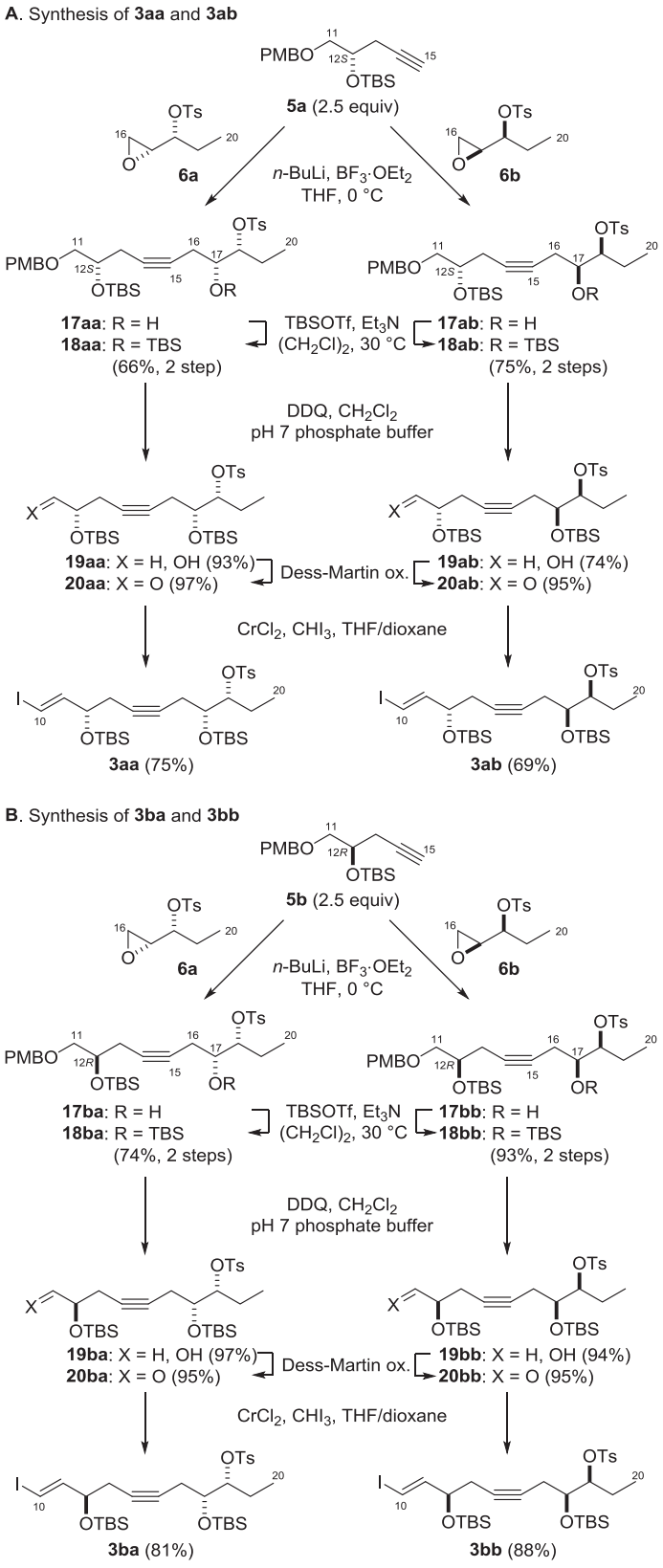
involved three transformations: i) chemoselective C16-tosylation (**9a**→**15a**), ii) nucleophilic epoxide formation (**15a**→**16a**), and iii) C18-tosylation (**16a**→**6a**). The same two steps transformed the enantiomeric diol **14b** into **6b**.[15]



Scheme 3. Synthesis of C16–20 fragments **6a** and **6b**.

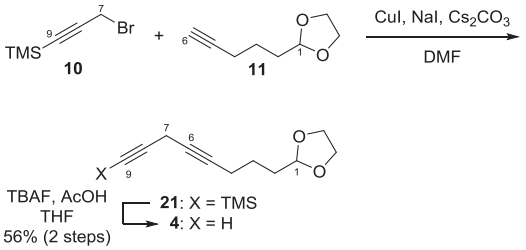
Scheme 4 illustrates the synthesis of the four C10–20 fragments **3aa**, **3ab**, **3ba** and **3bb** from the synthesized enantiomeric pairs **5a**/**5b** and **6a**/**6b**. $BF_3{\cdot}OEt_2$-activated S_N2 reaction of the lithiated species of C11-15 fragment (12*S*)-**5a** with C16-20 epoxides **6a** and **6b** at 0 °C produced **17aa** and **17ab**, respectively. In this reaction, in situ generated C17-lithium alkoxides did not participate in formation of the C17,18-epoxide, and the free C17-hydroxy group of **17aa**/**17ab** was generated after aqueous work-up. TBS-protection of C17-secondary alcohol **17aa**/**17ab** and subsequent removal of the PMB group gave rise to C11-primary alcohol **19aa**/**19ab**. After Dess-Martin oxidation of alcohol **19aa**/**19ab** to aldehyde **20aa**/**20ab**,[16] Takai's vinyl iodination[17] of **20aa**/**20ab** with iodoform and $CrCl_2$ in THF and dioxane[18] yielded *E*-vinyl iodide **3aa**/**3ab**.[19] This five-step reaction sequence also converted **6a** and **6b** into the two C10–20 fragments **3ba** and **3bb**, respectively, upon alternative use of **5b**.

Achiral C1–9 fragment **4** was prepared in two steps from propargyl bromide **10** and alkyne **11**[20] (Scheme 5). Propargyl bromide **10** was treated with the copper alkynide of C1–6 alkyne **11**,[21] giving rise to diyne **21**. The C9-TMS group of thus obtained **21** was removed using TBAF in the presence of AcOH to provide **4**. Of note, buffering with AcOH effectively suppressed deprotonation of the acidic double propargylic protons at C7, thereby preventing decomposition of the product **4**.



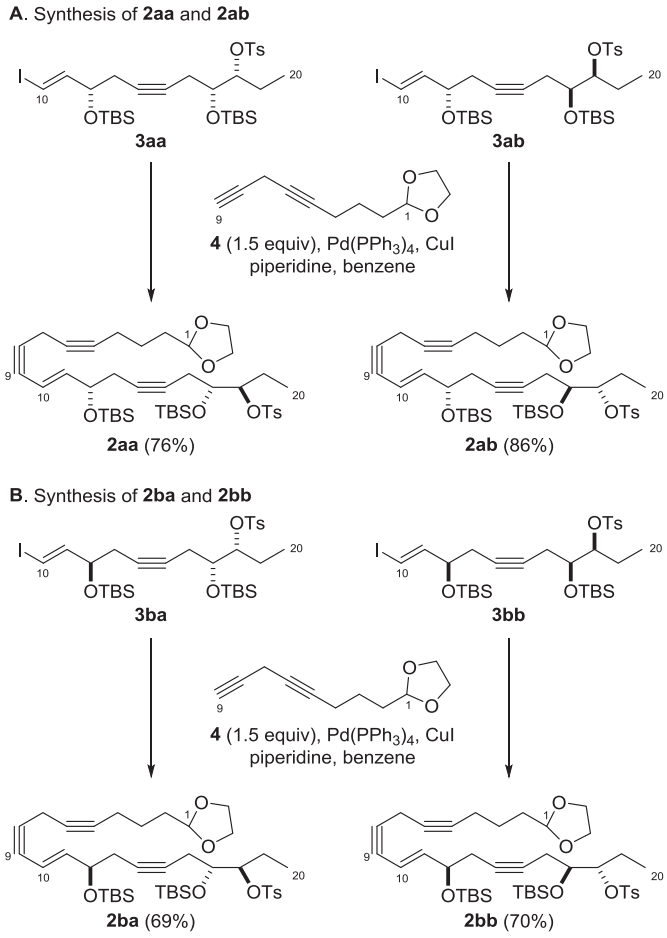
Scheme 4. Synthesis of the four C10–20 fragments **3aa**, **3ab**, **3ba**, and **3bb**.

The carbon backbone of **1** was then assembled by Sonogashira coupling between C10–20 fragments **3** and C1–9 fragment **4** (Scheme 6).[22] Separate treatment of the four stereoisomers **3aa**,



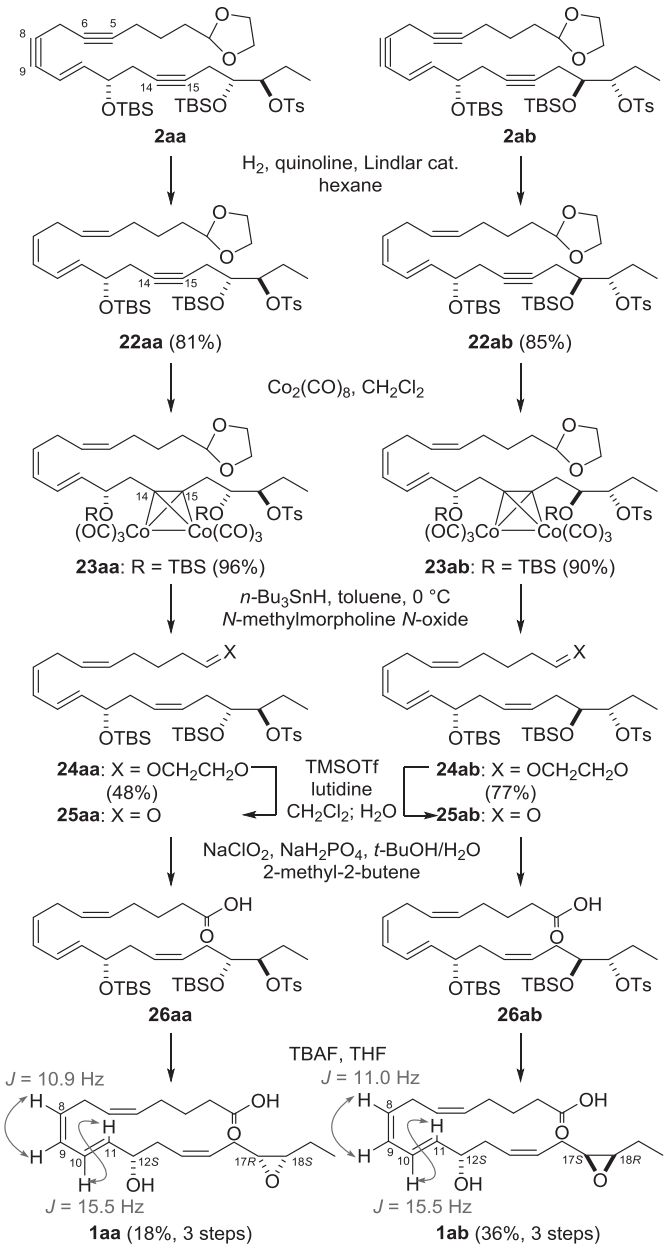
Scheme 5. Synthesis of the C1–9 fragment **4**.

3ab, **3ba** and **3bb** with **4** in the presence of catalytic $Pd(PPh_3)_4$ and CuI induced C–C bond formation to yield triynes **2aa**, **2ab**, **2ba** and **2bb**, respectively. Thus, the three S_N2-alkynylation reactions and one Sonogashira coupling reactions efficiently built the appropriately functionalized carbon skeleton of **1** from six simple units.



Scheme 6. Assembly of the carbon backbone of **1**.

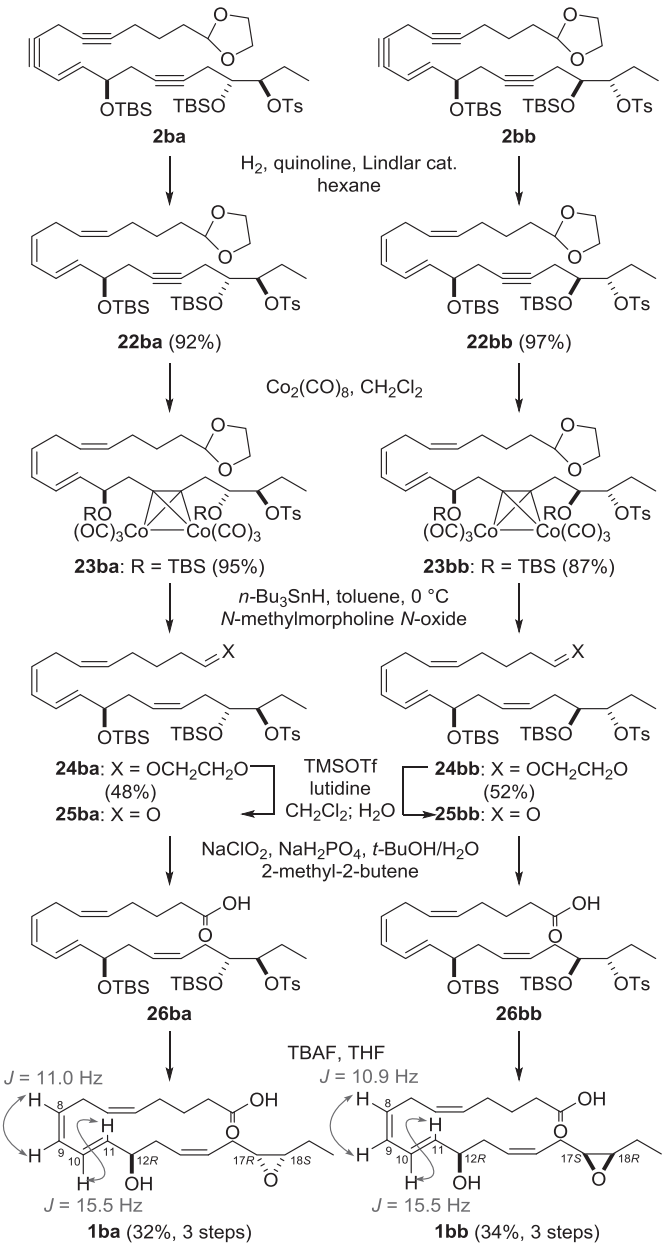
Next, we focused on reduction of the three internal alkynes (C5–6, C8–9, and C14–15) of **2aa** to the corresponding *Z*-alkenes of **24aa** without touching the preexisting *E*-alkene and generating *Z*-alkenes (Scheme 7). This transformation turned out to be challenging. Lindlar reduction[23] of triyne **2aa** in the presence of quinoline in hexane smoothly effected reduction of two of the three alkynes, leading to monoyne **22aa** with the two *Z*-alkenes. However, the most hindered C14–15 alkyne, surrounded by two proximal TBSO groups, was resistant to hydrogenation conditions. For instance, application of an excess amount of Lindlar catalyst or increasing the reaction time induced over-reduction of the less hindered alkenes prior to reduction of the remaining C14–15 alkyne of **22aa**. Hence, an alternative approach was required to realize high chemoselective reduction of the alkyne in the presence of multiple alkenes.



Scheme 7. Total synthesis of (12*S*,17*R*,18*S*)-**1aa** and (12*S*,17*S*,18*R*)-**1ab**.

Recently, we have modified the Isobe reduction[24] and developed a robust Co-complexation/decomplexation protocol for formation of the *Z*-alkene from the hindered alkyne.[25] This highly chemoselective method was applied to **22aa** (Scheme 7). The C14–15 alkyne of **22aa** was first converted to the alkyne-dicobalt hexacarbonyl complex with $Co_2(CO)_8$ to afford **23aa**. The Co-complex moiety of **23aa** was smoothly reduced to the *Z*-alkene by the action of *n*-Bu_3SnH (15 equiv) and *N*-methylmorpholine *N*-oxide (10 equiv) at 0 °C, delivering **24aa** with negligible formation of over-reduced compounds.[26] Moreover, the combination of the Lindlar and modified Isobe reductions was reliably applied to the stereoisomeric triyne **2ab**. Partial reduction of **2ab** with Lindlar catalyst produced **22ab**, which was then subjected to alkyne-dicobalt hexacarbonyl complex formation to furnish **23ab**. The subsequent reductive decomplexation under the above conditions gave rise to tetraene **24ab**.

The total synthesis of **1aa**/**1ab** was completed from the obtained tetraenes **24aa**/**24ab** (Scheme 7). The cyclic acetal of **24aa**/**24ab** was chemoselectively hydrolyzed in the presence of the two acid labile TBS ethers under Kita-Fujioka's conditions, leading to **25aa**/**25ab**.[27] Aldehyde **25aa**/**25ab** was then oxidized to carboxylic acid **26aa**/**26ab**. Finally, removal of the two TBS groups and formation of the C17,18-epoxide were simultaneously attained by treating with TBAF, transforming **26aa** and **26ab** into (12*S*,17*R*,18*S*)-**1aa** and (12*S*,17*S*,18*R*)-**1ab**, respectively. Hence, the chemically labile epoxide of **1aa**/**1ab** was constructed at the final step of the total synthesis via nucleophilic displacement of the C18-tosylate by the in situ formed C17-alkoxide. As illustrated in Scheme 8, the two diastereomeric triynes **2ba** and **2bb** were submitted to the same six-steps to produce (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**, respectively. The geometry of the conjugated *E*,*Z*-diene of **1aa**/**1ab**/**1ba**/**1bb** was confirmed from the H8–H9 and H10–H11 coupling constants, indicating its non-isomerization throughout the series of transformations from **22aa**/**22ab**/**22ba**/**22bb**. The total synthesis of the four isomers **1aa**, **1ab**, **1ba** and **1bb** allowed us to compare their retention times with that of the naturally occurring **1** using HPLC. As a result, the absolute structures of the EPA-derived natural lipids were established to be (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*R*,18*S*)-, and (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*S*,18*R*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa** and **1ab**).[9,28] Therefore, the natural forms were disclosed to be diastereomers at the C17,18-epoxide.



Scheme 8. Total synthesis of (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**.

A preliminary structure-activity relationship (SAR) study was performed using synthetic (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb** (Fig. 2). Specifically, the *anti*-inflammatory activities of these four compounds were evaluated using an in vivo inflammation model.[29] Zymosan A, a glucan from the yeast cell wall, was used to induce acute peritonitis in mice. Intravenous administration of as little as 1 ng of the 4 compounds blocked the infiltration of PMN leucocytes at 2 h in the inflamed peritoneal cavity, showing that all of the synthesized lipids possessed *anti*-inflammatory activity. Intriguingly, one of the natural forms, **1aa**, displayed more potent *anti*-inflammatory activity than the other natural form, **1ab**, and the activity of the unnatural compound **1ba** was stronger than those of natural **1ab** and unnatural **1bb**. These results together clarified the importance of the presence of the (17*R*,18*S*)-epoxide and the relative indifference of activity to the stereochemistry of the C12-hydroxy group.

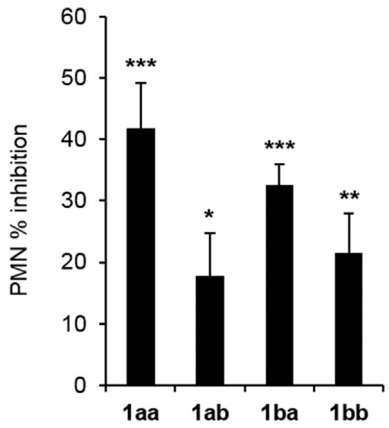


Fig. 2. Bioassay of synthetic **1aa**, **1ab**, **1ba** and **1bb**. The compounds (1 ng) were injected intravenously through the tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected, and the number of PMN leucocytes was counted. Values represent mean ± SE, n≥3, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ versus vehicle control.

3. Conclusion

We achieved the convergent total synthesis of the four stereoisomers of a new lipid mediator, (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid (**1**). The stereoisomers, (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**, were synthesized from **7a**/**7b**, **8**, **9a**/**9b**, **10**, **11** and iodoform in 15 longest linear steps and 18 overall steps. The key features of the synthesis route include: i) construction of the carbon backbone of **1** through three S_N2 alkynylation reactions and one Sonogashira coupling reaction and ii) chemoselective formation of three *Z*-alkenes by stepwise reduction using Lindlar reduction of the two alkynes (C5–6 and C8–9) and modified Isobe reduction of the remaining C14–15 alkyne. The fully synthetic construction of the four isomers allowed both determination of the EPA-derived natural lipid mediators to be **1aa** and **1ab** and evaluation of their *anti*-inflammatory activities. The biological data revealed the importance of the stereochemistry of the epoxide: the isomers with the (17*R*,18*S*)-epoxide (**1aa**, **1ba**) were more potent than the isomers (**1ab**, **1bb**)

with the (17*S*,18*R*)-epoxide. More detailed functional and biological analyses of the synthesized compounds will be our next focus.

4. Experimental section

4.1. General methods

All reactions sensitive to air or moisture were carried out in dry solvents under argon atmosphere, unless otherwise noted. THF, CH_2Cl_2 and toluene were purified by Glass Contour solvent dispensing system. Et_3N and piperidine were purified by distillation over CaH_2. $BF_3\cdot OEt_2$ was purified by distillation over P_2O_5. All other reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel [granular, neutral, 32–53 μm; spherical, carboxylic acid supported (Chromatorex-ACD COOH), 45–75 μm]. Medium pressure liquid chromatography was carried out by using a system equipped with a pre-packed silica gel 40 μm (14 g, 20×75 mm; 45 g, 26×150 mm). Melting points are reported uncorrected. Optical rotations were measured using the sodium D line. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using an FT/IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 or 500 MHz, and 100 or 150 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ for ^1H NMR (δ=7.26), $CDCl_3$ for ^{13}C NMR (δ=77.0), C_6HD_5 for ^1H NMR (δ=7.16), CD_2HOD for ^1H NMR (δ=3.31), and CD_3OD for ^{13}C NMR (δ=49.0) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. The carbon numbering of the synthetic compounds corresponds to that of **1**. High resolution mass spectra were measured on ESI-TOF or DART-TOF mass spectrometers.

*4.1.1. C11–15 fragment **5a**.* *n*-BuLi (1.35 M in hexane, 12.5 mL, 16.9 mmol) was added to a solution of trimethylsilyl acetylene **8** (2.3 mL, 16 mmol) in THF (34 mL) at −78 °C. The solution was stirred at −78 °C for 10 min, warmed to 0 °C and stirred for 50 min. After the mixture was cooled to −78 °C, $BF_3\cdot OEt_2$ (2.0 mL, 16 mmol) and a solution of **7a** (1.56 g, 8.04 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at −78 °C for 30 min and warmed to −40 °C over 1 h, and then saturated aqueous NH_4Cl solution (30 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 4/1) to afford the crude alcohol **12a**, which was used in the next reaction without further purification.

K_2CO_3 (1.44 g, 10.4 mmol) was added to a solution of the above crude alcohol **12a** in MeOH (62 mL) at room temperature. The reaction mixture was stirred at room temperature for 11 h. After the mixture was cooled to 0 °C, saturated aqueous NH_4Cl solution (10 mL) was added. The resultant mixture was extracted with Et_2O (60 mL ×4), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 4/1 to 1/1) to afford the crude alcohol, which was used in the next reaction without further purification.

TBSOTf (0.28 mL, 1.2 mmol) was added to a solution of the above crude alcohol and 2,6-lutidine (0.32 mL, 2.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to room temperature and stirred for 1.5 h, and then TBSOTf (0.40 mL, 1.7 mmol) and 2,6-lutidine (0.68 mL, 5.8 mmol) were added. After 20 min, TBSOTf (1.4 mL, 5.9 mmol) and 2,6-lutidine (1.3 mL, 11 mmol) were added. After further 40 min, TBSOTf (1.0 mL, 4.4 mmol) and 2,6-lutidine (0.70 mL, 6.0 mmol) were added again. The mixture was stirred for 10 min and cooled to 0 °C, and then saturated aqueous $NaHCO_3$ solution (10 mL) was added. The resultant mixture was extracted with Et_2O (60 mL ×3), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 7/1) to afford C11–15 fragment **5a** (2.61 g, 7.79 mmol) in 97% yield over three steps: colorless oil: $[\alpha]_D^{28}$ −0.60 (*c* 0.90, $CHCl_3$). The other analytical data of **5a** were identical to those of **5b**.

*4.1.2. C11–15 fragment **5b**.* According to the synthetic procedure of **5a**, C11–15 fragment **5b** (1.58 g, 4.73 mmol) was synthesized from **7b** (970 mg, 5.00 mmol) and trimethylsilyl acetylene **8** (1.4 mL, 9.9 mmol) in 95% yield over three steps by using *n*-BuLi (1.6 M in hexane, 6.6 mL, 11 mmol) and $BF_3\cdot OEt_2$ (1.2 mL, 9.7 mmol) in THF (25 mL) for the first reaction, K_2CO_3 (899 mg, 6.51 mmol) in MeOH (40 mL) for the second, and TBSOTf (1.3 mL, 5.7 mmol) and 2,6-lutidine (1.4 mL, 12 mmol) in CH_2Cl_2 (45 mL) for the third. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 5/1) for the first reaction, on silica gel (45 g, hexane/EtOAc 6/1 to 2/1) for the second and on silica gel (45 g, hexane to hexane/EtOAc 30/1) for the third: colorless oil; $[\alpha]_D^{27}$ +0.51 (*c* 1.1, $CHCl_3$); IR (neat) ν 3310, 2953, 2929, 2856, 2121, 1613, 1514, 1464, 1249, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.95 (1H, t, *J*=2.7 Hz, H15), 2.35 (1H, ddd, *J*=16.9, 6.0, 2.7 Hz, H13a), 2.47 (1H, ddd, *J*=16.9, 6.0, 2.7 Hz, H13b), 3.45 (1H, dd, *J*=14.2, 5.5 Hz, H11a), 3.47 (1H, dd, *J*=14.2, 5.5 Hz, H11b), 3.81 (3H, s, OMe), 3.96 (1H, tt, *J*=6.0, 5.5 Hz, H12), 4.47 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J*=8.7 Hz, aromatic), 7.26 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.6, 18.1, 24.7, 25.8 (×3), 55.3, 69.8, 70.2, 73.0, 73.3, 81.4, 113.7 (×2), 129.2 (×2), 130.4, 159.1; HRMS (ESI) calcd for $C_{19}H_{30}O_3SiNa$ 357.1856 $[M+Na]^+$, found 357.1862.

*4.1.3. Triol **9a**.* A solution of **14a** (3.71 g, 8.38 mmol, a 1.0:2.5:0.56:0.89 mixture of **14a**, *t*-BuOH, Et_2O and pentane) in THF (20 mL) was added to a suspension of $LiAlH_4$ (1.28 g, 33.7 mmol) in THF (65 mL) at 0 °C over 25 min. The reaction mixture was warmed to room temperature and stirred for 5 h. After the mixture was cooled to 0 °C, saturated aqueous potassium sodium tartrate solution (50 mL) and *n*-BuOH (100 mL) were added. The resultant mixture was warmed to room temperature and stirred for 19 h. After separation, the aqueous layer was extracted with *n*-BuOH (20 mL ×4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was performed by flash column chromatography on silica gel (30 g, $CHCl_3$/MeOH 9/1 to 5/1) to afford triol **9a** (783 mg, 6.51 mmol) in 78% yield: colorless oil. The analytical data of **9a** were identical to those reported previously.[12b]

*4.1.4. Triol **9b**.* According to the synthetic procedure of **9a**, triol **9b** (390 mg, 3.25 mmol) was synthesized from **14b** (1.00 g, 3.39 mmol, a 1.0:0.80:0.40:0.80 mixture of **14b**, *t*-BuOH, Et_2O and pentane) in 96% yield by using $LiAlH_4$ (520 mg, 13.7 mmol) in THF (36 mL). Purification was performed by flash column chromatography on silica gel (20 g, $CHCl_3$/MeOH 5/1): colorless oil. The other analytical data of **9b** were identical to those reported previously.[12b]

*4.1.5. C16–20 fragment **6a**.* NaH (60 wt % in mineral oil, 784 mg, 19.6 mmol) was added to a solution of **9a** (783 mg, 6.53 mmol) in THF (130 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at 0 °C for 50 min, warmed to room temperature, and stirred

for 40 min. After the mixture was cooled to 0 °C, NaH (60 wt % in mineral oil, 392 mg, 9.80 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1.5 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at room temperature for 17 h. After the mixture was cooled to 0 °C, pH 7 phosphate buffer (20 mL) was added. The resultant mixture was extracted with EtOAc (150 mL and 100 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 9/1) to afford C16–20 fragment **6a** (1.16 g, 4.53 mmol) in 69% yield: white solid; mp 61 °C; $[\alpha]_D^{18}$−16 (*c* 1.0, $CHCl_3$); IR (neat) ν 2976, 2935, 2886, 1598, 1459, 1358, 1189, 1174, 1097, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J*=7.4 Hz, H20), 1.76 (2H, qd, *J*=7.4, 6.4 Hz, H19), 2.44 (3H, s, C*H*$_3$ of Ts), 2.63 (1H, dd, *J*=4.6, 2.3 Hz, H16a), 2.78 (1H, dd, *J*=4.6, 4.6 Hz, H16b), 3.05 (1H, ddd, *J*=6.4, 4.6, 2.3 Hz, H17), 4.28 (1H, dt, *J*=6.4, 6.4 Hz, H18), 7.33 (2H, d, *J*=7.8 Hz, aromatic), 7.82 (2H, d, *J*=7.8 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 21.5, 25.0, 44.6, 52.3, 84.6, 127.7 (×2), 129.5 (×2), 134.0, 144.5; HRMS (ESI) calcd for $C_{12}H_{16}O_4SNa$ 279.0662 $[M+Na]^+$, found 279.0661.

*4.1.6. C16–20 fragment **6b**.* According to the synthetic procedure of **6a**, C16–20 fragment **6b** (549 mg, 2.14 mmol) was synthesized from **9b** (393 mg, 3.28 mmol) in 65% yield by using NaH (60 wt % in mineral oil, 789 mg, 19.7 mmol) and tosyl imidazole (2.97 g, 13.4 mmol) in THF (65 mL). Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1): white solid; mp 61–62 °C; $[\alpha]_D^{18}$+16 (*c* 1.0, $CHCl_3$). The other analytical data of **6b** were identical to those of **6a** and the previously reported data.[15]

*4.1.7. TBS ether **18aa**.* *n*-BuLi (1.35 M in hexane, 1.7 mL, 2.3 mmol) was added to a solution of **5a** (722 mg, 2.16 mmol) in THF (3.0 mL) at −78 °C. The solution was stirred at −78 °C for 15 min, warmed to 0 °C and stirred for 30 min. After the mixture was cooled to −78 °C, $BF_3\cdot OEt_2$ (0.27 mL, 2.2 mmol) and a solution of **6a** (221 mg, 0.863 mmol) in THF (1.3 mL) were successively added. The reaction mixture was stirred at −78 °C for 30 min, warmed to 0 °C and stirred for 2 h, and then saturated aqueous NH_4Cl solution (10 mL) was added. The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1 to 6/1 to 4/1 to 2/1) to afford the crude **17aa**, which was used in the next reaction without further purification.

TBSOTf (0.29 mL, 1.3 mmol) was added to a solution of the above crude **17aa** and Et_3N (0.44 mL, 3.1 mmol) in 1,2-dichloroethane (6.0 mL) at 0 °C. The reaction mixture was warmed to 30 °C and stirred for 1 h, and then TBSOTf (0.14 mL, 0.61 mmol) and Et_3N (0.13 mL, 0.93 mmol) were added. The reaction mixture was stirred for 20 min, and then was poured into saturated aqueous $NaHCO_3$ solution (15 mL). The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) to afford TBS ether **18aa** (401 mg, 0.570 mmol) in 66% over two steps: colorless oil; $[\alpha]_D^{24}$+17 (*c* 0.97, $CHCl_3$). The other analytical data of **18aa** were identical to those of **18bb**.

*4.1.8. TBS ether **18ab**.* According to the synthetic procedure of **18aa**, **18ab** (319 mg, 0.452 mmol) was synthesized from **5a** (504 mg, 1.50 mmol) and **6b** (155 mg, 0.605 mmol) in 75% yield over two steps by using *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.6 mmol) and $BF_3\cdot OEt_2$ (0.19 mL, 1.5 mmol) in THF (3.0 mL) for the first reaction, and TBSOTf (0.23 mL, 1.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in 1,2-dichloroethane (5.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{26}$−7.5 (*c* 1.1, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1614, 1514, 1463, 1363, 1250, 1177, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.065 (3H, s, C*H*$_3$ of TBS), 0.067 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.76 (1H, m, H19b), 2.14–2.43 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.42 (1H, dd, *J*=10.0, 5.5 Hz, H11a), 3.50 (1H, dd, *J*=10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.87–3.94 (2H, m, H12 and 17), 4.38 (1H, ddd, *J*=8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J*=8.7 Hz, aromatic), 7.26 (2H, d, *J*=8.7 Hz, aromatic), 7.32 (2H, d, *J*=8.7 Hz, aromatic), 7.80 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.61, −4.56, 10.1, 17.9, 18.2, 21.5, 21.6, 22.3, 25.0, 25.7 (×3), 25.8 (×3), 55.2, 70.8, 71.5, 73.0, 73.6, 78.4, 78.7, 85.5, 113.7 (×2), 127.8 (×2), 129.1 (×2), 129.7 (×2), 130.6, 134.3, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3470.

*4.1.9. TBS ether **18ba**.* According to the synthetic procedure of **18aa**, **18ba** (444 mg, 0.629 mmol) was synthesized from **5b** (711 mg, 2.12 mmol) and **6a** (219 mg, 0.855 mmol) in 74% yield over two steps by using *n*-BuLi (1.6 M in hexane, 1.4 mL, 2.2 mmol) and $BF_3\cdot OEt_2$ (0.26 mL, 2.1 mmol) in THF (4.3 mL) for the first reaction, and TBSOTf (0.38 mL, 1.66 mmol) and Et_3N (0.51 mL, 3.7 mmol) in 1,2-dichloroethane (6.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{24}$+7.4 (*c* 1.0, $CHCl_3$). The other analytical data of **18ba** were identical to those of **18ab**.

*4.1.10. TBS ether **18bb**.* According to the synthetic procedure of **18aa**, **18bb** (781 mg, 1.11 mmol) was synthesized from **5b** (988 mg, 2.95 mmol) and **6b** (306 mg, 1.20 mmol) in 93% yield over two steps by using *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) and $BF_3\cdot OEt_2$ (0.37 mL, 3.0 mmol) in THF (5.9 mL) for the first reaction, and TBSOTf (0.95 mL, 4.1 mmol) and Et_3N (1.4 mL, 10 mmol) in 1,2-dichloroethane (12 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1 to 3/1) for the first reaction, and on silica gel (10 g, hexane to hexane/EtOAc 20/1) for the second: colorless oil; $[\alpha]_D^{26}$−15 (*c* 1.4, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1920, 1613, 1514, 1463, 1364, 1250, 1177, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (6H, s, C*H*$_3$ of TBS ×2), 0.08 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.88 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.76 (1H, m, H19b), 2.13–2.37 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.41 (1H, dd, *J*=10.0, 6.0 Hz, H11a), 3.49 (1H, dd, *J*=10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.86–3.94 (2H, m, H12 and 17), 4.35 (1H, ddd, *J*=8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.86 (2H, d, *J*=8.2 Hz, aromatic), 7.26 (2H, d, *J*=8.2 Hz, aromatic), 7.32 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.64, −4.59, 10.1, 17.9, 18.1, 21.4, 21.6, 22.2, 25.0, 25.7 (×3), 25.8 (×3), 55.2, 70.8, 71.5, 72.9, 73.5, 78.4, 78.7, 85.5, 113.6 (×2), 127.8 (×2), 129.1 (×2), 129.7 (×2), 130.5, 134.2, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3469.

*4.1.11. Alcohol **19aa**.* DDQ (284 mg, 1.28 mmol) was added to a solution of **18aa** (584 mg, 0.828 mmol) in a mixture of CH_2Cl_2 (8.0 mL) and pH 7 phosphate buffer (0.8 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. After the

mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ solution (10 mL) was added. The resultant mixture was extracted with EtOAc (50 mL and 40 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) to afford alcohol **19aa** (449 mg, 0.767 mmol) in 93% yield: colorless oil; $[\alpha]_D^{25}$+25 (*c* 1.2, $CHCl_3$). The other analytical data of **19aa** were identical to those of **19bb**.

*4.1.12. Alcohol **19ab**.* According to the synthetic procedure of alcohol **19aa**, **19ab** (452 mg, 0.773 mmol) was synthesized from **18ab** (736 mg, 1.04 mmol) in 74% yield by using DDQ (402 mg, 1.81 mmol) in a mixture of CH_2Cl_2 (80 mL) and pH 7 phosphate buffer (8 mL). The residue was purified twice by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) and flash column chromatography on silica gel (15 g, hexane/EtOAc 20/1 to 6/1): colorless oil; $[\alpha]_D^{28}$−6.6 (*c* 2.0, $CHCl_3$); IR (neat) ν 3571, 2953, 2929, 2857, 1923, 1599, 1463, 1363, 1255, 1189, 1176, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 1.92 (1H, dd, *J*=6.4, 6.4 Hz, O*H*), 2.14–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.58 (1H, ddd, *J*=11.0, 7.3, 5.0 Hz, H11a), 3.67 (1H, ddd, *J*=11.0, 5.5, 3.6 Hz, H11b), 3.85 (1H, m, H12), 3.90 (1H, m, H17), 4.37 (1H, ddd, *J*=8.3, 8.3, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.80 (2H, d, *J*=8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.93, −4.85, −4.68, −4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (×3), 25.7 (×3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.4, 127.7 (×2), 129.7 (×2), 134.2, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2919.

*4.1.13. Alcohol **19ba**.* According to the synthetic procedure of alcohol **19aa**, **19ba** (420 mg, 0.718 mmol) was synthesized from **18ba** (523 mg, 0.742 mmol) in 97% yield by using DDQ (254 mg, 1.12 mmol) in a mixture of CH_2Cl_2 (7.0 mL) and pH 7 phosphate buffer (0.7 mL). The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$+8.9 (*c* 1.1, $CHCl_3$). The other analytical data of **19ba** were identical to those of **19ab**.

*4.1.14. Alcohol **19bb**.* According to the synthetic procedure of **19aa**, alcohol **19bb** (606 mg, 1.04 mmol) was synthesized from **18bb** (781 mg, 1.11 mmol) in 94% yield by using DDQ (279 mg, 1.23 mmol) in a mixture of CH_2Cl_2 (10 mL) and pH 7 phosphate buffer (1.0 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1), and three times by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 4/1; 45 g, hexane to hexane/EtOAc 4/1; 14 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{27}$−24 (*c* 0.91, $CHCl_3$); IR (neat) ν 3465, 2954, 2929, 2857, 1644, 1463, 1363, 1255, 1189, 1177, 1100, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J*=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 1.93 (1H, dd, *J*=7.3, 5.9 Hz, O*H*), 2.15–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.57 (1H, ddd, *J*=11.9, 7.3, 5.0 Hz, H11a), 3.68 (1H, ddd, *J*=11.9, 5.9, 3.6 Hz, H11b), 3.85 (1H, m, H17), 3.91 (1H, m, H12), 4.35 (1H, ddd, *J*=8.2, 8.2, 4.1 Hz, H18), 7.34 (2H, d, *J*=8.7 Hz, aromatic), 7.79 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.94, −4.86, −4.69, −4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (×3), 25.7 (×3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.5, 127.7 (×2), 129.7 (×2), 134.1, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2897.

*4.1.15. Aldehyde **20aa**.* Dess–Martin periodinane (493 mg, 1.16 mmol) was added to a suspension of alcohol **19aa** (445 mg, 0.761 mmol) and $NaHCO_3$ (625 mg, 7.44 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then H_2O (10 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (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 (20 g, hexane/EtOAc 9/1 to 4/1) to afford aldehyde **20aa** (431 mg, 0.739 mmol) in 97% yield: colorless oil; $[\alpha]_D^{24}$+12 (*c* 1.0, $CHCl_3$). The other analytical data of **20aa** were identical to those of **20bb**.

*4.1.16. Aldehyde **20ab**.* According to the synthetic procedure of aldehyde **20aa**, **20ab** (303 mg, 0.520 mmol) was synthesized from **19ab** (320 mg, 0.547 mmol) in 95% yield by using Dess–Martin periodinane (471 mg, 1.11 mmol) and $NaHCO_3$ (449 mg, 5.35 mmol) in CH_2Cl_2 (32 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 10 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{27}$−22 (*c* 1.6, $CHCl_3$); IR (neat) ν 2953, 2929, 2857, 1741, 1600, 1471, 1463, 1363, 1255, 1177, 1120, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.117 (3H, s, C*H*$_3$ of TBS), 0.122 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.20 (1H, dd, *J*=16.0, 7.8 Hz, H16a), 2.37 (1H, m, H16b), 2.45–2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=7.8, 4.6 Hz, H17), 4.08 (1H, td, *J*=6.4, 1.4 Hz, H12), 4.36 (1H, dt, *J*=9.2, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.80 (2H, d, *J*=8.2 Hz, aromatic), 9.63 (1H, t, *J*=1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.85, −4.78, −4.6, 10.1, 17.9, 18.2, 21.4, 21.6, 22.2, 23.5, 25.67 (×3), 25.69 (×3), 71.3, 76.1, 76.6, 79.8, 85.4, 127.8 (×2), 129.7 (×2), 134.2, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3011.

*4.1.17. Aldehyde **20ba**.* According to the synthetic procedure of aldehyde **20aa**, **20ba** (395 mg, 0.679 mmol) was synthesized from **19ba** (420 mg, 0.718 mmol) in 95% yield by using Dess–Martin periodinane (461 mg, 1.09 mmol) and $NaHCO_3$ (593 mg, 7.06 mmol) in CH_2Cl_2 (7.2 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 20 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{24}$+22 (*c* 1.7, $CHCl_3$). The other analytical data of **20ba** were identical to those of **20ab**.

*4.1.18. Aldehyde **20bb**.* According to the synthetic procedure of aldehyde **20aa**, **20bb** (577 mg, 0.990 mmol) was synthesized from **19bb** (606 mg, 1.04 mmol) in 95% yield by using Dess–Martin periodinane (887 mg, 2.09 mmol) and $NaHCO_3$ (832 mg, 9.90 mmol) in CH_2Cl_2 (10 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$−13 (*c* 0.83, $CHCl_3$); IR (neat) ν 2953, 2930, 2857, 1741, 1463, 1365, 1254, 1177, 1119, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.12 (6H, s, C*H*$_3$ of TBS ×2), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 2.19 (1H, ddt, *J*=16.5, 8.2, 2.3 Hz, H16a), 2.35 (1H, m, H16b), 2.45–2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.92 (1H, dt, *J*=7.3, 4.6 Hz, H17), 4.07 (1H, td, *J*=6.8, 1.4 Hz, H12), 4.34 (1H, dt, *J*=9.2, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic), 9.63 (1H, t, *J*=1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.92, −4.87, −4.82, −4.6, 10.1, 17.9, 18.2, 21.3, 21.6, 22.2, 23.4, 25.6 (×3), 25.7 (×3), 71.3, 76.0, 76.5, 79.7, 85.4, 127.8 (×2), 129.7 (×2), 134.1, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3020.

*4.1.19. C10–20 fragment **3aa**.* A solution of iodoform (676 mg, 1.72 mmol) and aldehyde **20aa** (431 mg, 0.739 mmol) in 1,4-dioxane (4.4 mL) was added to a suspension of $CrCl_2$ (629 mg,

5.11 mmol) in a mixture of THF (2.9 mL) and 1,4-dioxane (4.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then H_2O (5 mL) was added. The resultant mixture was extracted with Et_2O (15 mL ×3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified flash column chromatography on silica gel (25 g, hexane to hexane/CH_2Cl_2 1/1) to afford C10–20 fragment **3aa** (389 mg, 0.551 mmol) in 75% yield: colorless oil; $[\alpha]_D^{24}$+40 (*c* 1.3, $CHCl_3$). The other analytical data of **3aa** were identical to those of **3bb**.

*4.1.20. C10–20 fragment **3ab**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3ab** (244 mg, 0.346 mmol) was synthesized from aldehyde **20ab** (291 mg, 0.499 mmol) in 69% yield by using $CrCl_2$ (434 mg, 3.53 mmol) and iodoform (469 mg, 1.19 mmol) in a mixture of THF (2.0 mL) and 1,4-dioxane (6.2 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{27}$+12 (*c* 1.1, $CHCl_3$); IR (neat) ν 2954, 2929, 2857, 1600, 1463, 1363, 1255, 1189, 1177, 1098, 931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s, C*H*$_3$ of TBS ×2), 0.07 (6H, s, C*H*$_3$ of TBS ×2), 0.77 (3H, t, *J*=7.5 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.50 (1H, m, H19a), 1.76 (1H, m, H19b), 2.17–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=6.9, 4.5 Hz, H17), 4.18 (1H, m, H12), 4.37 (1H, dt, *J*=8.0, 4.0 Hz, H18), 6.32 (1H, dd, *J*=14.3, 1.8 Hz, H10), 6.66 (1H, dd, *J*=14.3, 5.2 Hz, H11), 7.34 (2H, d, *J*=8.6 Hz, aromatic), 7.80 (2H, d, *J*=8.6 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.95, −4.86, −4.81, −4.6, 10.2, 17.9, 18.1, 21.4, 21.6, 22.2, 25.68 (×3), 25.72 (×3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.4, 127.8 (×2), 129.7 (×2), 134.2, 144.5, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1952.

*4.1.21. C10–20 fragment **3ba**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3ba** (388 mg, 0.550 mmol) was synthesized from aldehyde **20ba** (395 mg, 0.677 mmol) in 81% yield by using $CrCl_2$ (591 mg, 4.84 mmol) and iodoform (636 mg, 1.61 mmol) in a mixture of THF (2.7 mL) and 1,4-dioxane (4.0 mL). Purification was performed by flash column chromatography on silica gel (20 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{26}$−7.9 (*c* 1.1, $CHCl_3$). The other analytical data of **3ba** were identical to those of **3ab**.

*4.1.22. C10–20 fragment **3bb**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3bb** (613 mg, 0.868 mmol) was synthesized from aldehyde **20bb** (577 mg, 0.990 mmol) in 88% yield by using $CrCl_2$ (836 mg, 6.80 mmol) and iodoform (903 mg, 2.29 mmol) in a mixture of THF (4.0 mL) and 1,4-dioxane (12.4 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{24}$−41 (*c* 1.0, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1917, 1600, 1463, 1363, 1255, 1188, 1177, 1098, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (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), 0.08 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.4 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.16–2.40 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=8.7, 4.5 Hz, H17), 4.19 (1H, m, H12), 4.35 (1H, dt, *J*=8.7, 4.1 Hz, H18), 6.31 (1H, dd, *J*=14.6, 1.4 Hz, H10), 6.66 (1H, dd, *J*=14.6, 5.5 Hz, H11), 7.34 (2H, d, *J*=8.7 Hz, aromatic), 7.80 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.94, −4.88, −4.81, −4.6, 10.2, 17.9, 18.2, 21.3, 21.6, 22.2, 25.68 (×3), 25.73 (×3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.5, 127.8 (×2), 129.7 (×2), 134.1, 144.6, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1923.

*4.1.23. C1–9 fragment **4**.* A mixture of CuI (287 mg, 1.51 mmol), NaI (227 mg, 1.51 mmol) and Cs_2CO_3 (491 mg, 1.51 mmol) was dried in vacuo at room temperature. After the mixture was cooled to 0 °C, a solution of propargy bromide **10** (0.27 mL, 1.67 mmol) in DMF (2.6 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **11** (332 mg, 1.80 mmol, a 1.0:0.27:0.30 mixture of **11**, Et_2O and pentane) in DMF (2.6 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. The resultant mixture was filtered through a pad of Celite with Et_2O. The filtrate was extracted with Et_2O (20 mL and 10 mL ×3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 20/1) to afford the crude **21**, which was used in the next reaction without further purification.

AcOH (0.21 mL, 3.7 mmol) and TBAF (1.0 M in THF, 3.7 mL, 3.7 mmol) were successively added to a solution of the above crude **21** in THF (50 mL) at −5 °C. The reaction mixture was stirred at −5 °C for 1 h, warmed to room temperature, and stirred for 2 h. Then saturated aqueous NH_4Cl solution (15 mL) was added. The resultant mixture was extracted Et_2O (50 mL), and the organic layer was 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 (15 g, hexane to hexane/EtOAc 20/1) to afford C1–9 fragment **4** (165 mg, 0.927 mmol) in 56% over two steps: colorless oil; IR (neat) ν 3288, 2953, 2882, 2233, 2124, 1473, 1455, 1435, 1414, 1312, 1135, 1033, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59–1.67 (2H, m, H3), 1.73–1.80 (2H, m, H2), 2.05 (1H, t, *J*=2.7 Hz, H9), 2.23 (2H, tt, *J*=7.3, 2.7 Hz, H4), 3.14 (2H, dt, *J*=2.7, 2.7 Hz, H7), 3.81–4.01 (4H, m, acetal), 4.87 (1H, t, *J*=4.6 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 18.4, 22.9, 32.7, 64.7 (×2), 68.4, 73.4, 78.7, 80.5, 104.0; HRMS (DART) calcd for $C_{11}H_{15}O_2$ 179.1067 $[M+H]^+$, found 179.1073.

*4.1.24. Triyne **2aa**.* A mixture of $Pd(PPh_3)_4$ (58.5 mg, 50.6 μmol), CuI (19.3 mg, 0.101 mmol), piperidine (0.10 mL, 1.0 mmol), and C10–20 fragment **3aa** (237 mg, 0.336 mmol) in benzene (2.5 mL) was added to a solution of **4** (90.6 mg, 0.509 mmol) in benzene (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. The resultant mixture was extracted with Et_2O (10 mL ×2) and EtOAc (10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1) to afford **2aa** (192 mg, 0.254 mmol) in 76% yield: pale yellow oil. Triyne **2aa** was immediately used in the next reaction due to its instability under air. The ^1H NMR spectrum of **2aa** was identical to that of **2bb**.

*4.1.25. Triyne **2ab**.* According to the synthetic procedure of triyne **2aa**, **2ab** (152 mg, 0.201 mmol) was synthesized from **3ab** (166 mg, 0.235 mmol) and **4** (63.4 mg, 0.356 mmol) in 86% yield by using $Pd(PPh_3)_4$ (41.0 mg, 35.5 μmol), CuI (13.5 mg, 70.9 mmol) and piperidine (70 μL, 0.71 mmol) in benzene (3.6 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 6/1). Triyne **2ab** was immediately used in the next reaction due to its instability under air: pale yellow oil; HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3828. The ^1H NMR spectrum of **2ab** was identical to that of **2ba**.

*4.1.26. Triyne **2ba**.* According to the synthetic procedure of triyne **2aa**, **2ba** (179 mg, 0.236 mmol) was synthesized from **3ba** (243 mg, 0.344 mmol) and **4** (92.2 mg, 0.518 mmol) in 69% yield by using $Pd(PPh_3)_4$ (60.0 mg, 51.9 μmol), CuI (20.3 mg, 0.106 mmol) and

piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 8 g, hexane to hexane/EtOAc 9/1). Triyne **2ba** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.03 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.82 (3H, t, J=7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.53 (1H, m, H19a), 1.58–1.65 (2H, m, H3), 1.75–1.81 (3H, m, H2 and H19b), 1.86 (3H, s, CH_3 of Ts), 2.03 (2H, tt, J=6.9, 2.3 Hz, H4), 2.24–2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, J=1.8, 1.8 Hz, H7), 3.29–3.38 (2H, m, acetal), 3.45–3.54 (2H, m, acetal), 4.17 (1H, dt, J=6.8, 4.6 Hz, H17), 4.27 (1H, dt, J=5.5, 5.0 Hz, H12), 4.69 (1H, ddd, J=8.7, 4.6 Hz, H18), 4.73 (1H, t, J=5.0 Hz, H1), 5.94 (1H, ddt, J=16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, J=16.0, 5.0 Hz, H11), 6.75 (2H, d, J=8.2 Hz, aromatic), 7.83 (2H, d, J=8.2 Hz, aromatic).

*4.1.27. Triyne **2bb**.* According to the synthetic procedure of triyne **2aa**, **2bb** (181 mg, 0.240 mmol) was synthesized from **3bb** (242 mg, 0.342 mmol) and **4** (91.2 mg, 0.512 mmol) in 70% yield by using $Pd(PPh_3)_4$ (59.4 mg, 51.4 μmol), CuI (19.6 mg, 0.103 mmol) and piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 30 g, hexane to hexane/EtOAc 9/1). Triyne **2bb** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 0.03 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.81 (3H, t, J=7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.58–1.65 (2H, m, H3), 1.75–1.81 (3H, m, H2 and H19b), 1.86 (3H, s, CH_3 of Ts), 2.03 (2H, tt, J=6.9, 2.3 Hz, H4), 2.24–2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, J=1.8, 1.8 Hz, H7), 3.29–3.38 (2H, m, acetal), 3.45–3.54 (2H, m, acetal), 4.17 (1H, dt, J=6.8, 4.6 Hz, H17), 4.27 (1H, dt, J=5.5, 5.0 Hz, H12), 4.69 (1H, ddd, J=8.7, 4.6 Hz, H18), 4.73 (1H, t, J=5.0 Hz, H1), 5.93 (1H, ddt, J=16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, J=16.0, 5.0 Hz, H11), 6.75 (2H, d, J=8.2 Hz, aromatic), 7.83 (2H, d, J=8.2 Hz, aromatic); HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3819.

*4.1.28. Alkyne **22aa**.* A suspension of triyne **2aa** (108 mg, 0.143 mmol), quinoline (0.20 mL, 1.7 mmol) and Lindlar catalyst (222 mg) in hexane (10 mL) was stirred at room temperature for 15 min under H_2 atmosphere (1 atm). Lindlar catalyst (50–100 wt %) was added in every 5–10 min until triyne **2aa** and the diyne intermediate were disappeared on TLC (540 mg of Lindlar catalyst was added in total). The reaction mixture was filtered through a pad of Celite with hexane, and the filtrate was concentrated. The residue was dissolved in EtOAc (15 mL). The resultant solution was washed with aqueous 0.2 M HCl solution (10 mL ×2), aqueous saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1) to afford alkyne **22aa** (88.2 mg, 0.116 mmol) in 81% yield: colorless oil; $[\alpha]_D^{25}$+38 (*c* 0.97, $CHCl_3$). The other analytical data of **22aa** were identical to those of **22bb**.

*4.1.29. Alkyne **22ab**.* According to the synthetic procedure of **22aa**, **22ab** (64.0 mg, 84.2 μmol) was synthesized from **2ab** (75.3 mg, 99.6 μmol) in 85% yield by using quinoline (0.14 mL, 1.2 mmol) and Lindlar catalyst (330 mg) in hexane (7.5 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$+15 (*c* 0.93, $CHCl_3$); IR (neat) ν 2953, 2928, 2856, 1599, 1471, 1462, 1364, 1257, 1177, 1099, 932 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, CH_3 of TBS), 0.07 (6H, s, CH_3 of TBS ×2), 0.08 (3H, s, CH_3 of TBS), 0.76 (3H, t, J=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.63–1.70 (2H, m, H2), 1.76 (1H, m, H19b), 2.11 (2H, dt, J=7.3, 7.3 Hz, H4), 2.20–2.28 (2H, m, H13a and H16a), 2.33–2.41 (2H, m, H13b and H16b), 2.44 (3H, s, CH_3 of Ts), 2.92 (2H, m, H7), 3.82–3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.93–3.98 (2H, m, acetal), 4.30 (1H, dt, J=6.0, 6.0 Hz, H12), 4.37 (1H, ddd, J=8.7, 8.7, 3.6 Hz, H18), 4.85 (1H, t, J=5.0 Hz, H1), 5.33–5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, J=15.1, 5.0 Hz, H11), 6.00 (1H, dd, J=11.0, 11.0 Hz, H9), 6.45 (1H, dd, J=15.1, 11.0 Hz, H10), 7.33 (2H, d, J=8.7 Hz, aromatic), 7.80 (2H, d, J=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, -4.8, -4.61, -4.56, 10.1, 18.0, 18.3, 21.4, 21.6, 22.3, 23.9, 25.7 (×3), 25.8 (×3), 26.1, 27.0, 29.0, 33.4, 64.8 (×2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (×2), 128.0, 129.7 (×2), 129.9, 130.0, 134.3, 135.5, 144.5, one ^{13}C peak overlaps with other peaks; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4099.

*4.1.30. Alkyne **22ba**.* According to the synthetic procedure of **22aa**, **22ba** (84.3 mg, 0.111 mmol) was synthesized from **2ba** (91.1 mg, 0.120 mmol) in 92% yield by using quinoline (0.17 mL, 1.4 mmol) and Lindlar catalyst (462 mg) in hexane (9.0 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$−15 (*c* 1.4, $CHCl_3$). The other analytical data of **22ba** were identical to those of **22ab**.

*4.1.31. Alkyne **22bb**.* According to the synthetic procedure of **22aa**, **22bb** (96.0 mg, 0.126 mmol) was synthesized from **2bb** (98.1 mg, 0.130 mmol) in 97% yield by using quinoline (0.18 mL, 1.6 mmol) and Lindlar catalyst (800 mg) in hexane (10 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{24}$−37 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1461, 1364, 1254, 1177, 931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, CH_3 of TBS), 0.066 (3H, s, CH_3 of TBS), 0.071 (3H, s, CH_3 of TBS), 0.09 (3H, s, CH_3 of TBS), 0.76 (3H, t, J=7.5 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.64–1.70 (2H, m, H2), 1.75 (1H, m, H19b), 2.11 (2H, dt, J=7.4 Hz, H4), 2.15–2.29 (2H, m, H13a and H16a), 2.32–2.39 (2H, m, H13b and H16b), 2.44 (3H, s, CH_3 of Ts), 2.92 (2H, m, H7), 3.83–3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.94–3.98 (2H, m, acetal), 4.30 (1H, dt, J=6.0, 5.7 Hz, H12), 4.36 (1H, dt, J=9.0, 4.0 Hz, H18), 4.85 (1H, t, J=5.0 Hz, H1), 5.33–5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, J=15.0, 5.5 Hz, H11), 6.00 (1H, dd, J=11.0, 11.0 Hz, H9), 6.54 (1H, dd, J=15.0, 11.0 Hz, H10), 7.33 (2H, d, J=8.5 Hz, aromatic), 7.80 (2H, d, J=8.5 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, −4.64, −4.59, 10.1, 17.9, 18.2, 21.4, 21.6, 22.3, 23.9, 25.7 (×3), 25.8 (×3), 26.0, 27.0, 29.0, 33.3, 64.8 (×2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (×2), 127.9, 129.7 (×2), 129.9, 130.0, 134.2, 135.5, 144.5, one ^{13}C peak overlaps with other peaks; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4117.

*4.1.32. Complex **23aa**.* $Co_2(CO)_8$ (175 mg, 0.512 mmol) was added to a solution of **22aa** (98.2 mg, 0.129 mmol) in CH_2Cl_2 (2.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1) to afford alkyne-dicobalt hexacarbonyl complex **23aa** (130 mg, 0.124 mmol) in 96% yield: brown oil. The ^{1}H NMR spectrum of **23aa** was identical of that of **23bb**.

*4.1.33. Complex **23ab**.* According to the synthetic procedure of complex **23aa**, **23ab** (146 mg, 0.139 mmol) was synthesized from **22ab** (117 mg, 0.154 mmol) in 90% yield by using $Co_2(CO)_8$ (342 mg, 1.00 mmol) in CH_2Cl_2 (3.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3

of TBS), 0.10 (6H, s, CH_3 of TBS ×2), 0.11 (3H, s, CH_3 of TBS), 0.79 (3H, t, *J*=7.3 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45–1.55 (1H, m, H19a), 1.58–1.70 (4H, m, H2 and H3), 1.73 (1H, qd, *J*=7.4, 5.9 Hz, H19b), 2.09 (2H, dt, *J*=7.3, 6.8 Hz, H4), 2.44 (3H, s, CH_3 of Ts), 2.83 (1H, dd, *J*=16.5, 4.6 Hz, H16a), 2.88 (2H, m, H7), 3.14 (1H, dd, *J*=15.5, 3.2 Hz, H13a), 3.22 (1H, dd, *J*=15.5, 8.2 Hz, H13b), 3.35 (1H, dd, *J*=16.5, 6.4 Hz, H16b), 3.80–3.89 (2H, m, acetal), 3.92–3.99 (2H, m, acetal), 4.01 (1H, m, H17), 4.42 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J*=5.0 Hz, H1), 5.29–5.43 (3H, m, H5, H6 and H8), 5.73 (1H, dd, *J*=15.6, 6.9 Hz, H11), 5.99 (1H, dd, *J*=11.4, 11.4 Hz, H9), 6.56 (1H, dd, *J*=15.6, 11.4 Hz, H10), 7.31 (2H, d, *J*=8.3 Hz, aromatic), 7.79 (2H, d, *J*=8.3 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2482.

4.1.34. Complex ***23ba****.* According to the synthetic procedure of complex **23aa**, **23ba** (129 mg, 0.123 mmol) was synthesized from **22ba** (99 mg, 0.130 mmol) in 95% yield by using $Co_2(CO)_8$ (192 mg, 0.561 mmol) in CH_2Cl_2 (2.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil. The ^{1}H NMR spectrum of **23ba** was identical of that of **23ab**.

4.1.35. Complex ***23bb****.* According to the synthetic procedure of complex **23aa**, **23bb** (118 mg, 0.113 mmol) was synthesized from **22bb** (96 mg, 0.13 mmol) in 87% yield by using $Co_2(CO)_8$ (185 mg, 0.541 mmol) in CH_2Cl_2 (2.5 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 20/1 to 9/1): brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3 of TBS), 0.09 (3H, s, CH_3 of TBS), 0.10 (6H, s, CH_3 of TBS ×2), 0.79 (3H, t, *J*=7.5 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.49 (2H, dq, *J*=7.5, 7.5 Hz, H19), 1.57–1.77 (4H, m, H2 and H3), 2.08 (2H, dt, *J*=7.4, 7.4 Hz, H4), 2.44 (3H, s, CH_3 of Ts), 2.80–2.92 (3H, m, H7 and H16a), 3.12 (1H, dd, *J*=16.0, 8.6 Hz, H13a), 3.28 (1H, dd, *J*=16.0, 2.9 Hz, H13b), 3.37 (1H, dd, *J*=16.6, 6.9 Hz, H16b), 3.80–3.86 (2H, m, acetal), 3.90–3.96 (2H, m, acetal), 3.97 (1H, m, H17), 4.44 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J*=4.6 Hz, H1), 5.30–5.42 (3H, m, H5, H6 and H8), 5.74 (1H, dd, *J*=15.5, 6.9 Hz, H11), 5.97 (1H, dd, *J*=11.5, 11.5 Hz, H9), 6.58 (1H, dd, *J*=15.5, 11.5 Hz, H10), 7.32 (2H, d, *J*=8.6 Hz, aromatic), 7.79 (2H, d, *J*=8.6 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2445.

4.1.36. Tetraene ***24aa****.* *n*-Bu_3SnH (505 μL, 1.88 mmol) and *N*-methylmorpholine *N*-oxide (146 mg, 1.25 mmol) were successively added to a solution of alkyne dicobalt hexacarbonyl complex **23aa** (130 mg, 0.124 mmol) in toluene (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min under air, and then aqueous saturated KF (10 mL) was added. The resultant mixture was extracted with Et_2O (30 mL ×2), and the combined organic layers were washed with aqueous saturated KF (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography [a column consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 5 g, pentane to pentane/EtOAc 9/1] to afford tetraene **24aa** (45.4 mg, 0.0596 mmol) in 48% yield: colorless oil; $[\alpha]_D^{24}$+24 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2928, 2956, 1462, 1366, 1254, 1189, 1177, 1073 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.74 (3H, t, *J*=7.8 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45–1.56 (3H, m, H3 and H19a), 1.63–1.71 (2H, m, H2), 1.77 (1H, m, H19b), 1.98–2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, CH_3 of Ts), 2.91 (2H, m, H7), 3.79 (1H, ddd, *J*=9.2, 4.1, 4.1 Hz, H17), 3.82–3.89 (2H, m, acetal), 3.91–3.99 (2H, m, acetal), 4.18 (1H, dt, *J*=6.4, 6.4 Hz, H12), 4.30 (1H, dt, *J*=9.2, 4.1 Hz, H18), 4.85 (1H, t, *J*=4.6 Hz, H1), 5.30–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.64 (1H, dd, *J*=15.1, 6.4 Hz, H11), 5.97 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.47 (1H, dd, *J*=15.1, 11.0 Hz, H10), 7.33 (2H, d, *J*=8.3 Hz, aromatic), 7.79 (2H, d, *J*=8.3 Hz, aromatic). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.75, −4.71, −4.6, −4.4, 10.3, 17.9, 18.2, 21.0, 21.6, 23.9, 25.7 (×3), 25.9 (×3), 26.0, 27.0, 29.1, 33.4, 36.5, 64.8 (×2), 72.3, 72.9, 86.2, 104.5, 124.4, 127.5, 127.6, 127.8 (×2), 127.9, 128.1, 129.6, 129.7 (×2), 130.0, 134.3, 136.6, 144.5.

4.1.37. Tetraene ***24ab****.* According to the synthetic procedure of tetraene **24aa**, **24ab** (81.4 mg, 0.107 mmol) was synthesized from **23ab** (146 mg, 0.139 mmol) in 77% yield by using *n*-Bu_3SnH (0.56 mL, 2.1 mmol) and *N*-methylmorpholine *N*-oxide (164 mg, 1.40 mmol) in toluene (68 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g, hexane to hexane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{27}$−4.2 (*c* 0.85, $CHCl_3$); IR (neat) ν 2955, 2929, 2857, 1921, 1599, 1471, 1463, 1366, 1258, 1189, 1177, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.75 (3H, t, *J*=7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.63–1.70 (2H, m, H2), 1.77 (1H, m, H19b), 1.98–2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, CH_3 of Ts), 2.91 (2H, t, *J*=6.3 Hz, H7), 3.78 (1H, ddd, *J*=8.6, 4.0, 4.0 Hz, H17), 3.82–3.86 (2H, m, acetal), 3.92–3.99 (2H, m, acetal), 4.18 (1H, dt, *J*=6.9, 5.8 Hz, H12), 4.31 (1H, dt, *J*=8.6, 4.0 Hz, H18), 4.85 (1H, t, *J*=4.5 Hz, H1), 5.31–5.48 (5H, m, H5, H6, H8, H14 and H15), 5.64 (1H, dd, *J*=14.9, 5.8 Hz, H11), 5.97 (1H, dd, *J*=10.9, 10.9 Hz, H9), 6.46 (1H, dd, *J*=14.9, 10.9 Hz, H10), 7.33 (2H, d, *J*=8.0 Hz, aromatic), 7.79 (2H, d, *J*=8.0 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.75, −4.71, −4.6, −4.4, 10.3, 17.8, 18.2, 21.0, 21.6, 23.9, 25.7 (×3), 25.9 (×3), 26.0, 27.0, 29.2, 33.4, 36.5, 64.8 (×2), 72.2, 72.7, 86.2, 104.5, 124.3, 127.5, 127.6, 127.8 (×2), 127.9, 128.1, 129.6, 129.7 (×2), 130.0, 134.3, 136.6, 144.5; HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4254.

4.1.38. Tetraene ***24ba****.* According to the synthetic procedure of tetraene **24aa**, **24ba** (45.0 mg, 59.1 μmol) was synthesized from **23ba** (129 mg, 0.123 mmol) in 48% yield by using *n*-Bu_3SnH (0.49 mL, 1.8 mmol) and *N*-methylmorpholine *N*-oxide (141 mg, 1.21 mmol) in toluene (60 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 6 g and 10% (w/w) KF contained silica gel 2 g, pentane to pentane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{23}$+2.9 (*c* 1.2, $CHCl_3$). The other analytical data of **24ba** were identical to those of **24ab**.

4.1.39. Tetraene ***24bb****.* According to the synthetic procedure of tetraene **24aa**, **24bb** (45.1 mg, 59.2 μmol) was synthesized from **23bb** (118 mg, 0.113 mmol) in 52% yield by using *n*-Bu_3SnH (0.45 mL, 1.7 mmol) and *N*-methylmorpholine *N*-oxide (133 mg, 1.14 mmol) in toluene (55 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g, pentane to pentane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{25}$−26 (*c* 0.83, $CHCl_3$); HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4259. The other analytical data of **24bb** were identical to those of **24aa**.

4.1.40. (12S,17R,18S)- ***1aa****.* TMSOTf (0.16 mL, 0.86 mmol) was added to a solution of **24aa** (42.9 mg, 56.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 15 min, and then H_2O (2.0 mL) and EtOAc (2.0 mL) were successively added. The resultant solution was warmed to room temperature and stirred for 30 min. After separation, the organic layer was washed with aqueous 0.1 M HCl solution (10 mL ×2), aqueous saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude aldehyde **25aa**, which was used in the next reaction without further purification.

A solution of $NaClO_2$ (80 wt %, 56.3 mg, 0.498 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (82.5 mg, 0.529 mmol) in H_2O (0.6 mL) was added

to a solution of the above crude aldehyde **25aa** in a mixture of *t*-BuOH (0.6 mL) and 2-methyl-2-butene (0.6 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, and then diluted with H_2O (5 mL). The resultant solution was extracted with EtOAc (10 mL), and the organic layer was washed with H_2O (4 mL) and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) to afford the crude carboxylic acid **26aa**, which was used in the next reaction without further purification.

TBAF (1.0 M in THF, 0.56 mL, 0.56 mmol) was added to a solution of the above crude carboxylic acid **26aa** in THF (1.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. After 0.1 M HCl solution (4 mL) was added, the mixture was extracted with EtOAc (10 mL and 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) to afford the crude **1aa**. The crude **1aa** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=36 min) to afford **1aa** (3.5 mg, 10 μmol) in 18% yield over three steps: colorless oil; $[\alpha]_D^{25}$+3.4 (*c* 0.18, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074. The other analytical data of **1aa** were identical to those of **1bb**.

*4.1.41. (12S,17S,18R)-**1ab**.* According to the synthetic procedure of **1aa**, **1ab** (12.3 mg, 36.8 μmol) was synthesized from **24ab** (78 mg, 0.102 mmol) in 36% yield over three steps by using TMSOTf (0.28 mL, 1.6 mmol) and 2,6-lutidine (0.27 mL, 2.3 mmol) in CH_2Cl_2 (2.0 mL) for the first reaction, $NaClO_2$ (80 wt %, 107 mg, 0.946 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (152 mg, 0.974 mmol) in a mixture of *t*-BuOH (1.0 mL), 2-methyl-2-butene (1.0 mL) and H_2O (1.0 mL) for the second, and TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) in THF (2.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=34 min) for the third. Aldehyde **25ab**: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J*=7.3 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.43–1.82 (3H, m, H3 and H19a), 1.65–1.80 (3H, m, H2 and H19b), 2.00–2.24 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.91 (2H, t, *J*=7.8 Hz, H7), 3.78 (1H, m, H17), 4.19 (1H, dt, *J*=6.0, 5.5 Hz, H12), 4.30 (1H, dt, *J*=8.7, 4.1 Hz, H18), 5.29–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J*=15.1, 6.0 Hz, H11), 5.98 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.46 (1H, dd, *J*=15.1, 11.0 Hz, H10), 7.33 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic), 9.77 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.73, −4.66, −4.5, 10.3, 17.8, 18.2, 21.0, 21.6, 21.9, 25.7 (×3), 25.8 (×3), 26.0, 26.4, 29.1, 36.4, 43.2, 72.1, 72.7, 86.2, 124.2, 127.4, 127.6, 127.7 (×2), 128.2, 128.7, 129.0, 129.2, 129.7 (×2), 134.3, 136.8, 144.5, 202.3; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.4034. (12*S*,17*S*,18*R*)-**1ab**: colorless oil; $[\alpha]_D^{25}$−4.7 (*c* 0.18, $CHCl_3$); IR (neat) ν 3424, 3009, 2968, 2931, 2877, 2856, 1714, 1438, 1409, 1236, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J*=7.5 Hz, H20), 1.57 (2H, qd, *J*=7.5, 6.3 Hz, H19), 1.73 (2H, br s, H3), 2.18 (2H, br s, H4), 2.21–2.38 (6H, m, H2, H13 and H16), 2.91 (1H, td, *J*=6.3, 4.6 Hz, H18), 2.93–3.00 (2H, m, H7 and H17), 4.18 (1H, dt, *J*=6.3, 6.3 Hz, H12), 5.34–5.46 (3H, m, H5, H6 and H8), 5.53–5.62 (2H, m, H14 and H15), 5.69 (1H, dd, *J*=15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.57 (1H, dd, *J*=15.5, 11.0 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 27.0, 27.3, 27.8, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.3, 130.5, 130.9, 137.1, the C1, C2 and C3 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074; UV (MeOH) λ_{max} 236 nm (ε 2.17×10^4).

*4.1.42. (12R,17R,18S)-**1ba**.* According to the synthetic procedure of **1aa**, **1ba** (6.25 mg, 18.7 μmol) was synthesized from **24ba** (45.0 mg, 59.0 mmol) in 32% yield over three steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first reaction, $NaClO_2$ (80 wt %, 61.0 mg, 0.540 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (88.0 mg, 0.564 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=35 min) for the third: colorless oil; $[\alpha]_D^{24}$+7.6 (*c* 0.31, MeOH); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2046. The other analytical data of **1ba** were identical to those of **1ab**.

*4.1.43. (12R,17S,18R)-**1bb**.* According to the synthetic procedure of **1aa**, **1bb** (6.64 mg, 19.9 μmol) was synthesized from **24bb** (45.1 mg, 59.2 mmol) in 34% yield over three steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first reaction, $NaClO_2$ (80 wt %, 60.9 mg, 0.539 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (85.7 mg, 0.549 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=35 min) for the third. Aldehyde **25bb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (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), 0.73 (3H, t, *J*=7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.44–1.60 (3H, m, H3 and H19a), 1.70–1.80 (3H, m, H2 and H19b), 2.00–2.28 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.90 (2H, m, H7), 3.79 (1H, m, H17), 4.19 (1H, dt, *J*=6.3, 5.8 Hz, H12), 4.29 (1H, m, H18), 5.29–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J*=15.5, 5.8 Hz, H11), 5.98 (1H, dd, *J*=11.5, 10.9 Hz, H9), 6.47 (1H, dd, *J*=15.5, 11.5 Hz, H10), 7.32 (2H, d, *J*=8.0 Hz, aromatic), 7.79 (2H, d, *J*=8.0 Hz, aromatic), 9.77 (1H, s, H1). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.73, -4.69, -4.63, -4.4, 10.3, 17.9, 18.2, 20.9, 21.6, 21.9, 25.7 (×3), 25.9 (×3), 26.0, 26.5, 29.1, 36.5, 43.3, 72.3, 72.9, 86.2, 124.3, 127.4, 127.7, 127.8 (×2), 128.2, 128.7, 129.1, 129.2, 129.7 (×2), 134.3, 136.8, 144.6, 202.4; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.3996. (12*R*,17*S*,18*R*)-**1bb**: colorless oil; $[\alpha]_D^{24}$−4.1 (*c* 0.36, MeOH); IR (neat) ν 3416, 3010, 2966, 2927, 2875, 2854, 1714, 1565, 1437, 1409, 1260, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J*=7.5 Hz, H20), 1.57 (2H, qd, *J*=7.5, 6.3 Hz, H19), 1.68 (2H, br s, H3), 2.15 (2H, m, H4), 2.20–2.40 (6H, m, H2, H13 and H16), 2.90–3.00 (4H, m, H7, H17 and H18), 4.18 (1H, dt, *J*=6.3, 6.3 Hz, H12), 5.34–5.41 (3H, m, H5, H6 and H8), 5.53–5.61 (2H, m, H14 and H15), 5.69 (1H, dd, *J*=15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J*=10.9, 10.9 Hz, H9), 6.57 (1H, ddt, *J*=15.5, 10.9, 1.2 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 26.1, 27.0, 27.3, 27.6, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.4, 130.4, 130.9, 137.1, the C1 and C2 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$, found 333.2059; UV (MeOH) λ_{max} 236 nm (ε 2.35×10^4).

4.2. Bioassay

Peritonitis was induced as described in Ref. 29. Synthetic **1aa**, **1ab**, **1ba** and **1bb** (each 1 ng) were injected intravenously through

tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected, PMN leukocyte numbers were counted, cell viability was determined using Trypan blue exclusion, and differential cell counts were monitored by Wright-Giemsa staining.

4.3. Statistical analysis

Results are expressed as means±SE. Differences between two groups were tested by the Student's *t*-test. Multiple comparisons were analyzed using ANOVA followed by Tukey test. A significance level of $P<0.05$, $P<0.01$ and $P<0.001$ was used.

Associated content

NMR spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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