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Total Synthesis of Four Stereoisomers of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-Dihydroxy-4,7,10,12,16,18-docosahexaenoic Acid and Their Anti-inflammatory Activities

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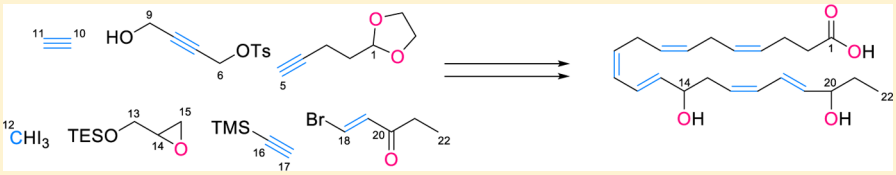
Supporting Information



ABSTRACT: A novel anti-inflammatory lipid mediator, (4*Z*,7*Z*,10*Z*,12*E*,14*S*,16*Z*,18*E*,20*R*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid (**1aa**), and its three C14,C20 stereoisomers (**1ab,ba,bb**) were synthesized in a convergent fashion. The carbon backbone of the target compounds was assembled from seven simple fragments by employing two Sonogashira coupling and three S_N2 alkynylation reactions. The thus constructed four internal alkynes were chemoselectively reduced to the corresponding (*Z*)-alkenes by applying a newly developed stepwise protocol: (i) hydrogenation of the three alkynes using Lindlar catalyst and (ii) formation of the dicobalt hexacarbonyl complex from the remaining alkyne and subsequent reductive decomplexation. The synthetic preparation of the stereochemically defined four isomers **1aa,ab,ba,bb** permitted determination of the absolute structure of the isolated natural product to be **1aa**. Biological testing of the four synthetic 14,20-dihydroxydocosahexaenoic acids disclosed similar anti-inflammatory activities of the non-natural isomers (**1ab,ba,bb**) and the natural form (**1aa**).

INTRODUCTION

Endogenous lipid mediators control acute or innate inflammatory response toward microorganisms or tissue injury and play an important role in the active resolution phase of inflammation for protecting organs from collateral damage.[1] Metabolites of omega-3 polyunsaturated fatty acids (e.g., docosahexaenoic acid (DHA)) have attracted significant attention as lipid mediators, as they exhibit in vivo anti-inflammatory activities (Figure 1).[2,3] Maresin 1[4] is a representative lipid mediator, and its intriguing structural features, such as a (*E*,*E*,*Z*)-triene and two allylic hydroxy groups, are biosynthetically constructed from DHA.

The structure determination of these biologically important lipid mediators has been highly challenging. Whereas UV spectroscopic and LC-MS/MS analyses are effective in deducing planar structures of lipid mediators, stereochemical assignments of the double bonds and hydroxy groups by detailed NMR analyses have been hampered due to the scarce availability of lipid mediators from natural sources. Accordingly, practical preparation of all the stereoisomers by stereoselective total synthesis is necessary in order to establish the absolute structure of the lipid mediators.[5,6]

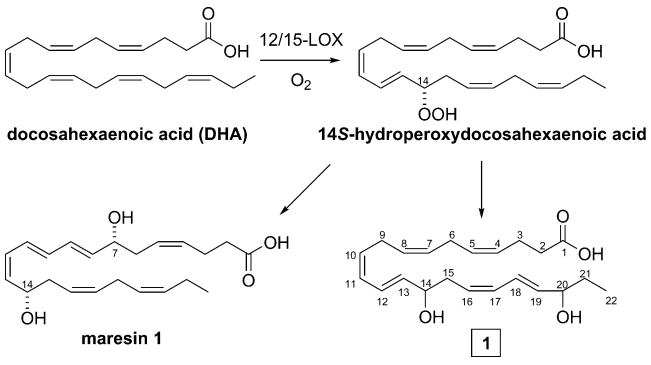


Figure 1. Structures of DHA and anti-inflammatory active lipid mediators and the possible biosynthetic pathway of maresin 1 and **1** from DHA.

Recently, we identified a novel anti-inflammatory metabolite of DHA (**1**; Figure 1), produced by eosinophils during the resolution phase of a mouse acute inflammation model.[7]

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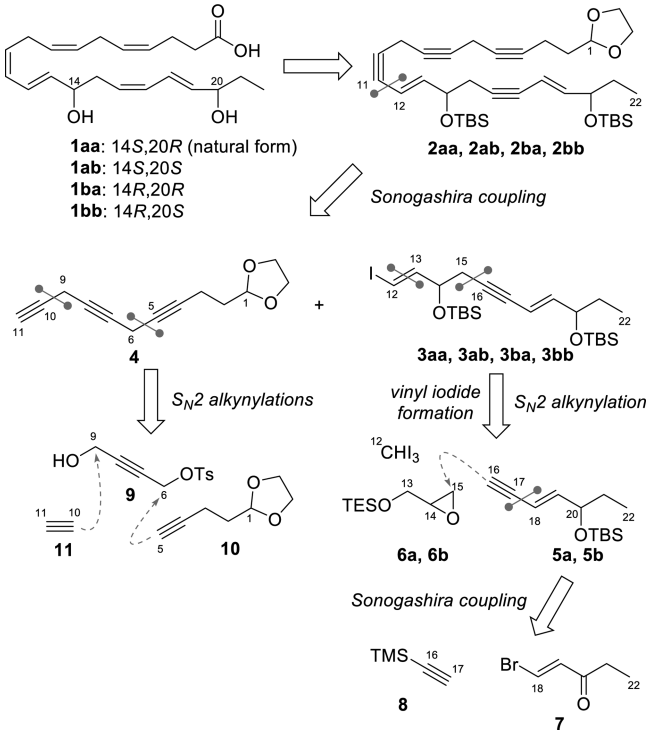
Biological tests revealed that nanomolar concentrations of **1** inhibited infiltration of polymorphonuclear (PMN) leukocytes in a zymosan-induced mouse peritonitis model. The planar structure of **1** was tentatively assigned as (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid from UV and LS-MS/MS analysis of the minute amount of sample available. *E* regiochemistries at C12 and C18 were also suggested from the biogenetic oxidation pathway of **1**. Additionally, the C14 configuration of **1** was speculated to be *S*, because biosynthetic production of both **1** and maresin 1 was shown to involve 12/15-lipoxygenase (LOX)-promoted oxidation of DHA to 14*S*-hydroperoxydocosahexaenoic acid.[4a,7]

We set about unambiguously establishing the absolute structure of naturally occurring **1** by synthesizing the four possible stereoisomers at the C14- and C20-hydroxy groups. Here we report the detailed stereoselective total synthesis of the four stereoisomers of **1**, (14*S*,20*R*)-, (14*S*,20*S*)-, (14*R*,20*R*)-, and (14*R*,20*S*)-14,20-dihydroxydocosahexaenoic acids (**1aa**,**ab**,**ba**,**bb**; Scheme 1). HPLC analysis of the natural

Scheme 1. Synthetic Plan of the Four Stereoisomers of 1



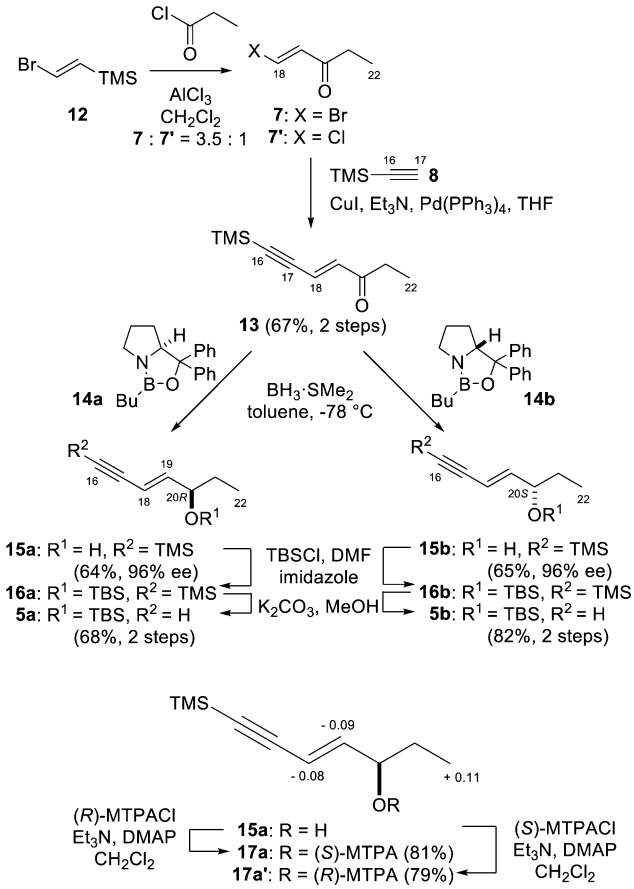
and synthetic compounds established the absolute structure of natural **1** to be **1aa** with the 14*S*,20*R* configuration. Furthermore, a structure–activity relationship (SAR) study of the four isomers disclosed similar anti-inflammatory activities of the synthesized natural (**1aa**) and non-natural compounds (**1ab**,**ba**,**bb**).

RESULTS AND DISCUSSION

To establish a unified synthetic route to the four stereoisomers of 14,20-dihydroxydocosahexaenoic acid (**1aa**,**ab**,**ba**,**bb**), we designed a convergent strategy using two chiral fragments (**5a**/**5b**, **6a**/**6b**), three achiral fragments (**9**–**11**), and iodoform (Scheme 1). 14,20-Dihydroxydocosahexaenoic acid (**1**) was first retrosynthetically converted to tetrayne **2**, which possesses the four internal alkynes as surrogates of the requisite (*Z*)-alkenes of **1**. Compound **2** was dissected into the halves **3** and **4**. In the synthetic direction, Sonogashira coupling between C12–C22 vinyl iodide **3** and the copper alkynide of triyne **4** was envisioned to furnish the carboskeleton of **2**. C12–C22 vinyl iodide **3** could be synthesized by S_N2 alkynylation of the lithium alkynide of **5** and TES-protected glycidol **6** and subsequent vinyl iodide formation with iodoform. The four stereoisomers **3aa**,**ab**,**ba**,**bb** of **3** could be synthesized in enantiopure form by combining the enantiomeric pairs **5a**/**5b** and **6a**/**6b**. Chiral **5a**/**5b** was to be prepared through two-carbon elongation by Sonogashira coupling between **7** and **8** and subsequent asymmetric reduction of the C20-ketone. On the other hand, achiral triyne **4** could be synthesized from **9** by sequential S_N2 alkynylation of the copper acetylides generated from **10** and **11**.

The synthesis began with preparation of enantiomers **5a**,**b** from **7** (Scheme 2). Compound **7** was obtained as an inseparable mixture with **7′** (**7**:**7′** = 3.5:1) by $AlCl_3$-promoted acylation of **12** with propionyl chloride.[8] The mixture was subjected to Sonogashira coupling using TMS-acetylene **8**, CuI, and $Pd(PPh_3)_4$ to produce the C16–C22 carbon chain **13**.[9] The chiral complex of $BH_3{\cdot}SMe_2$ and (*S*)-2-butyl-CBS-oxazaborolidine **14a** in turn induced the asymmetric reduction

Scheme 2. Synthesis of C16–C22 Fragments 5a,b through Asymmetric Reduction and Determination of the Absolute Stereochemistry of the C20 Position[a]



[a]The values on the lowermost structure are the differences ($\Delta\delta$) in ^{1}H chemical shifts between **17a** and **17a′** ($\Delta\delta = \delta(\mathbf{17a}) - \delta(\mathbf{17a'})$) in $CDCl_3$.

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of the C20-ketone of **13** to produce the optically active **15a** in 96% ee.[10,11] Protection of the C20-hydroxy group of **15a** as its TBS ether, followed by removal of the C16-TMS group under basic conditions, afforded the requisite C16−C22 fragment (20*R*)-**5a**. Alternative use of (*R*)-2-butyl-CBS-oxazaborolidine **14b** in the reduction of **13** led to **15b** (96% ee), which was converted to the C16−C22 fragment (20*S*)-**5b** using the above two-step protocol. The C20 absolute configurations of **5a**,**b** were established by application of the modified Mosher method to **15a**.[12] Namely, **15a** was transformed to (*S*)-MTPA ester **17a** and (*R*)-MTPA ester **17a′**. The difference in the ^{1}H NMR chemical shifts between **17a** and **17a′** confirmed the 20*R*-configuration of **15a**.

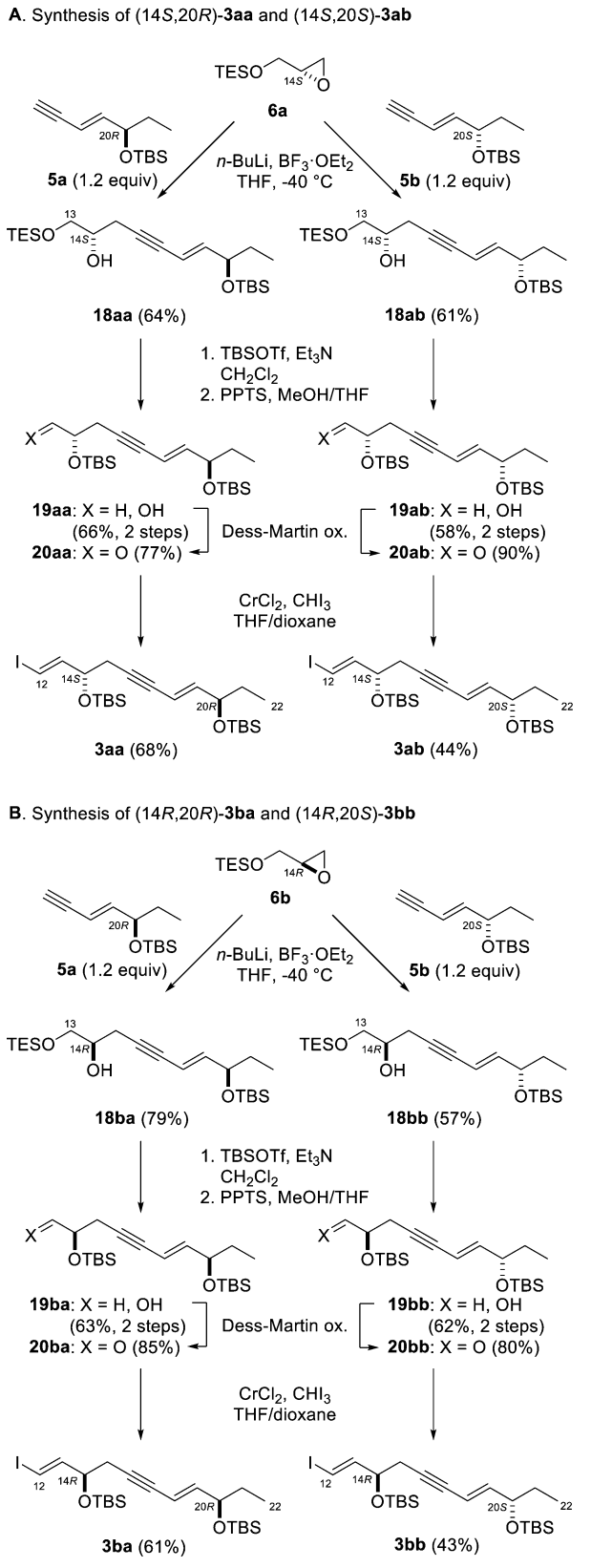
Parts A and B of Scheme 3 show the synthesis of the four C12−C22 fragments **3aa**,**ab**,**ba**,**bb**. The lithium alkynides, which were prepared from (20*R*)-**5a** and (20*S*)-**5b** using *n*-BuLi, reacted with TES-protected glycidol (14*S*)-**6a**[13] in the presence of $BF_3{\cdot}OEt_2$, resulting in formation of (14*S*,20*R*)-**18aa** and (14*S*,20*S*)-**18ab**, respectively.[14] The obtained **18aa**,**ab** were transformed to aldehydes **20aa**,**ab**, respectively, by the following three steps: (i) TBS protection of the C14-hydroxy group, (ii) chemoselective removal of the TES group, and (iii) Dess−Martin oxidation[15] of the resulting C13-primary alcohol. Next, treatment of aldehydes **20aa**,**ab** with CHI_3 and $CrCl_2$[16] in THF and 1,4-dioxane[17] resulted in formation of the (*E*)-vinyl iodide of C12−C22 fragments (14*S*,20*R*)-**3aa** and (14*S*,20*S*)-**3ab**, respectively.[18] The stereoisomers (14*R*,20*R*)-**3ba** and (14*R*,20*S*)-**3bb** were synthesized by following the same five-step transformation from TES-protected glycidol (14*R*)-**6b**.

C1−C11 fragment **4** was synthesized from the known **9**[19] and **10**[20] through two Cu-mediated S_N2 alkynylations (Scheme 4). The copper alkynide was formed from C1−C5 alkyne **10** by the action of CuI and Cs_2CO_3[21] and attached on C6 of propargyl tosylate **9** to produce C1−C9 diyne **21**. The C9-hydroxy group of **21** was then converted to the corresponding bromide by treatment with CBr_4 and $(PPh_2CH_2)_2$.[22] The second S_N2 alkynylation between **22** and ethynylcopper, derived from ethynylmagnesium bromide **11′** and CuCl, furnished C1−C11 triyne **4**.

Next, the entire carbon backbone of **1** was assembled by Sonogashira coupling between the four stereoisomeric C12−C22 fragments and the C1−C11 fragment (Scheme 5). Compounds **3aa**,**ab**,**ba**,**bb** were separately subjected to C1−C11 fragment **4** (1.2−1.5 equiv) and CuI in the presence of catalytic $Pd(PPh_3)_4$, delivering tetraynes **2aa**,**ba**,**ab**,**bb**, respectively. Hence, a series of C−C bond formations using metal alkynides successfully transformed the simple fragments into the functionalized carbon structure of **1** bearing the four triple bonds.

The most challenging task in the synthesis of **1** was reduction of the four alkynes to the corresponding *Z*-alkenes, because the chemoselective reductions should be realized without over-reduction of the C12−C13 and C18−C19 (*E*)-alkenes and the generating (*Z*)-alkenes (Scheme 6). To achieve the requisite conversion, reagents and conditions were tuned using **2aa** as the substrate. Lindlar reduction[23] of **2aa** in the presence of quinoline in hexane at room temperature resulted in generation of a mixture of desired hexaene **23aa** (30% yield) and over-reduced products.[24] Contamination of **23aa** with the over-reduced byproducts at this stage was found to be problematic. Purification of the final product **1aa** was not possible using various chromatographic methods when the contaminated **23aa** was subjected to the last three steps.[25] Thus, further efforts to produce pure **23aa** were pursued. Optimization of the amount of Lindlar catalyst (300 wt %), quinoline (12 equiv), reaction time (100 min), and temperature (0 °C) allowed selective reduction of three (C4−C5, C7−C8, and C10−C11) of the

Scheme 3. Synthesis of Four C12−C22 Fragments 3aa,ab,ba,bb



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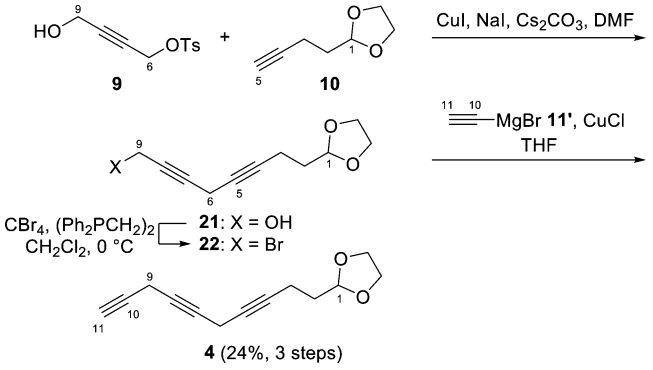
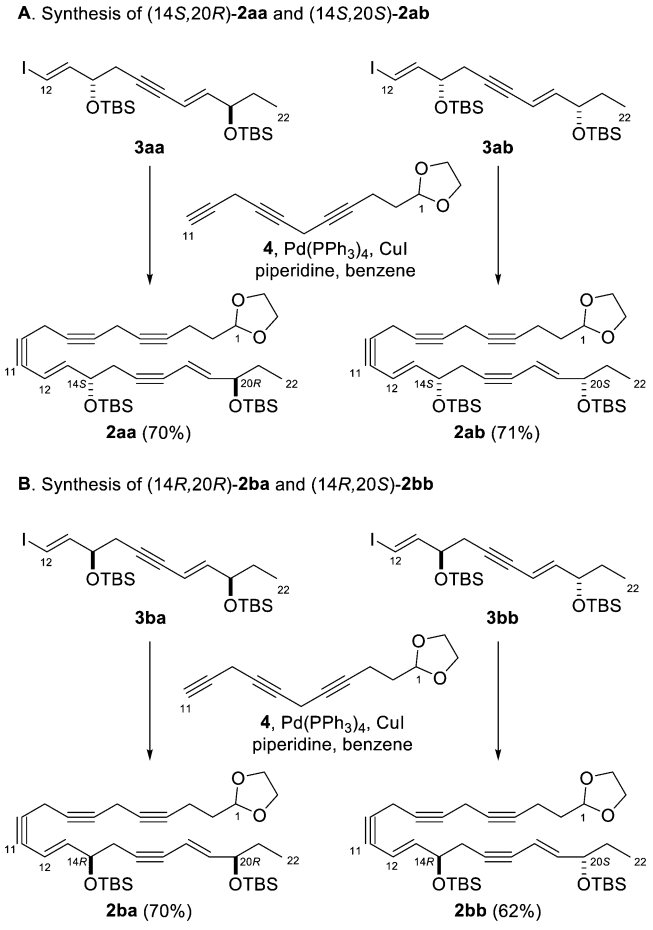
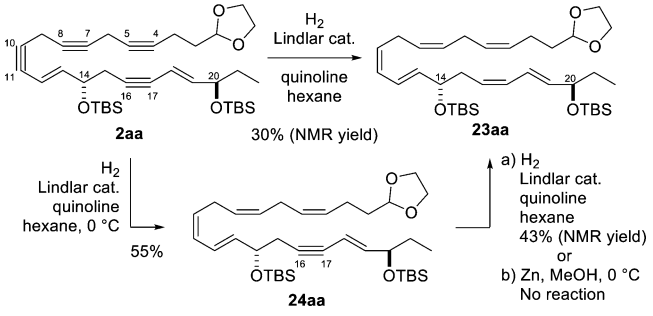
Scheme 4. Synthesis of C1−C11 Triyne 4



Scheme 5. Assembly of the Carbon Backbone of 1



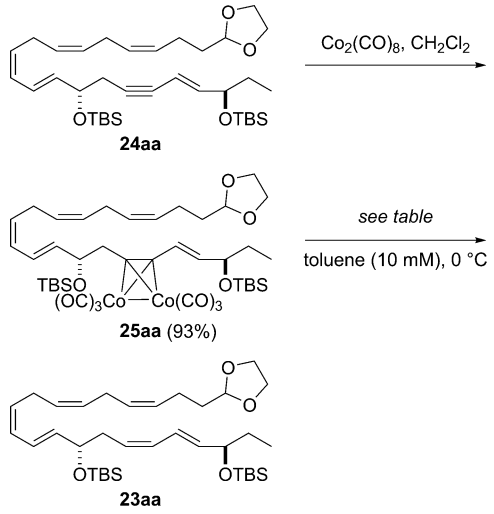
Scheme 6. Chemoselective Reduction of Tetrayne 2aa to Monoyne 24aa



four alkynes to generate pure **24aa**. Consequently, the C16−C17 alkyne, sterically protected by the neighboring bulky C14-TBS ether, was more resistant to hydrogenation than the other three triple bonds. Indeed, reduction of the remaining C16−C17 alkyne of **24aa** with Lindlar catalyst under more forceful conditions only produced a mixture of **23aa** and over-reduced products, while the alternative use of Cu/Ag-activated Zn in MeOH[26] with **24aa** did not induce the requisite reduction.

A more powerful yet chemoselective method was required to obtain pure **23aa** from **24aa**. Numerous unsuccessful attempts to hydrogenate **24aa** led us to note the mechanistically distinct reductive protocol reported by Isobe and co-workers.[27,28] They demonstrated that treatment of alkyne dicobalt hexacarbonyl complexes with *n*-Bu_3SnH at elevated temperature afforded the corresponding (*Z*)-alkenes. This protocol was indeed applicable to transformation of **24aa** to **23aa** (Table 1). The alkyne

Table 1. Synthesis of Hexaene 23aa by Isobe Reduction[a]



entry	reductant	additive	temp, °C	yield, %
1	*n*-Bu_3SnH	none	65	41[b]
2	*n*-Bu_3SnH	*N*-methylmorpholine oxide	0	86
3	Ph_3SnH	*N*-methylmorpholine oxide	0	94
4	$(TMS)_3SiH$	*N*-methylmorpholine oxide	0	18[c]
5[d]	$NaH_2PO_2·H_2O$	*N*-methylmorpholine oxide	0	48[b]

[a]Conditions: **25aa** (1 equiv), reductant (15 equiv), additive (10 equiv), toluene (10 mM), 0 °C. [b]Yield was calculated by ^1H NMR analysis of a mixture of **23aa**, **24aa**, and over-reduced compounds. [c]Yield was calculated by ^1H NMR analysis of a mixture of **23aa**, **24aa**, and hydrosilylated products. [d]Methoxyethanol was used as a solvent.

dicobalt hexacarbonyl complex **25aa** was first prepared by treatment of **24aa** with $Co_2(CO)_8$ and then was submitted to the original conditions (*n*-Bu_3SnH (10 equiv), 65 °C, toluene, entry 1),[27] leading to hexaene **23aa** in 41% yield. Despite generation of **23aa**, the reaction suffered from decomposition and over-reduction. Thus, milder reaction conditions needed to be realized by accelerating the reductive decomplexation step.

N-Methylmorpholine oxide is known to increase the rate of the Pauson−Khand reaction of an alkyne dicobalt hexacarbonyl complex.[29] It is widely accepted that reaction between an amine oxide and cobalt-coordinating carbon monoxide generates a coordinately unsaturated cobalt species, which triggers the Pauson−Khand reaction at low temperature.[30] Accordingly, we speculated that *N*-methylmorpholine oxide would strongly promote the reductive decomplexation of **25aa** through

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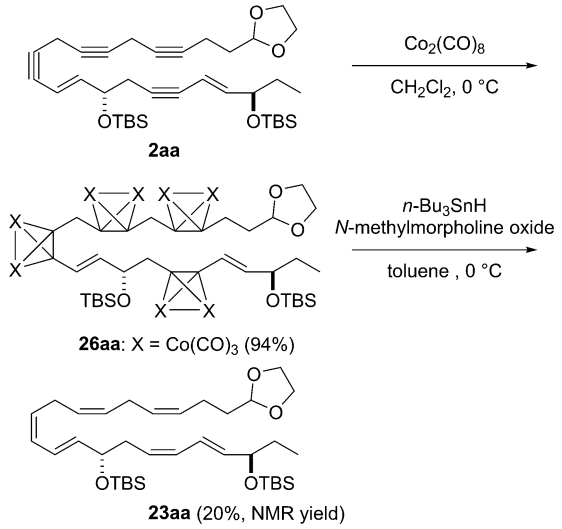
decarbonylation of the complex.[31] When *N*-methylmorpholine oxide (10 equiv) was added to the reaction mixture (Table 1, entry 2), the reaction of **25aa** proceeded at 0 °C to afford pure **23aa** in 86% yield. Importantly, no decomposition of **23aa**/**24aa** or over-reduction was observed under these conditions. Screening of the reductants clarified that *n*-Bu_3SnH and Ph_3SnH (entries 2 and 3) were superior to $(TMS)_3SiH$ and $NaH_2PO_2{\cdot}H_2O$[32] (entries 4 and 5). Because residual Ph_3SnH could not be separated from **23aa**, entry 2 was chosen as the optimized conditions for synthesis of pure hexaene **23aa**.

Thus, a combination of the Lindlar reduction and modified Isobe reaction successfully converted tetrayne **2aa** to pure hexaene **23aa** by the intermediacy of monoyne **24aa**. It is noteworthy that direct application of tetrayne **2aa** to the Co-complexation/decomplexation protocol was much less effective (Scheme 7). Although complex **26aa** was smoothly formed

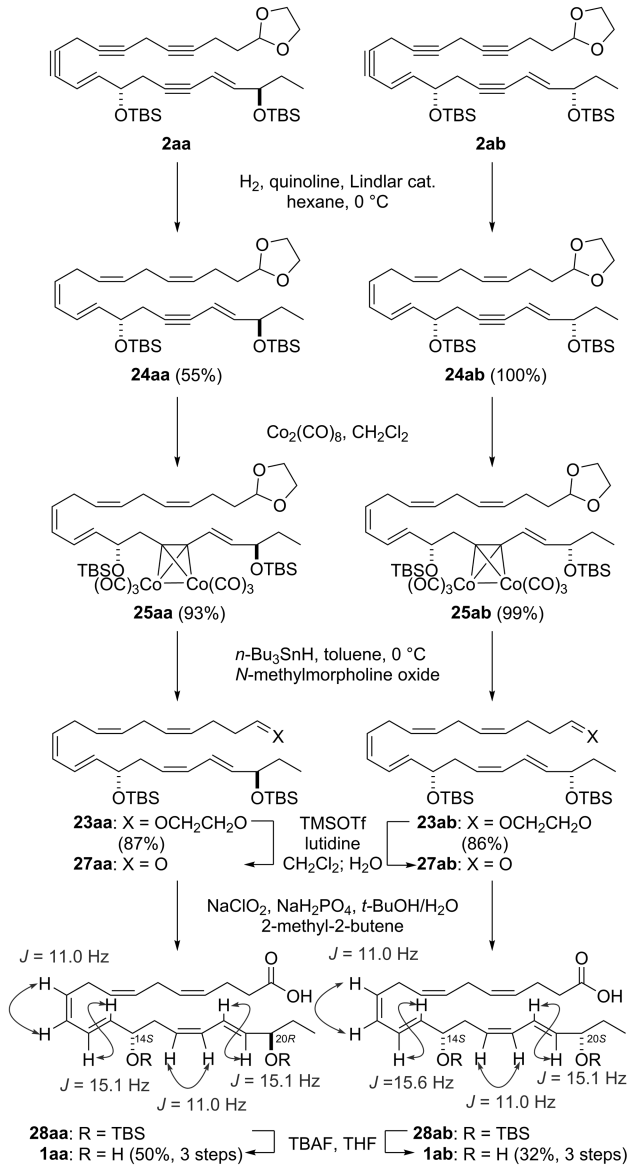
Scheme 7. Attempted Isobe Reduction of 2aa



from **2aa** and $Co_2(CO)_8$, reductive decomplexation of **26aa** using *n*-Bu_3SnH and *N*-methylmorpholine oxide produced **23aa** in only poor yield along with the over-reduced products. The observed byproducts were attributable to reduction of the less sterically shielded olefins by in situ generated cobalt hydride species.[33]

As with **2aa**, the optimized Lindlar and Isobe reductions were applied to stereoisomer tetrayne **2ab** (Scheme 8). Hydrogenation of tetrayne **2ab** produced monoyne **24ab**, which was then converted to the alkyne dicobalt hexacarbonyl complex and treated with *n*-Bu_3SnH and *N*-methylmorpholine oxide to provide **23ab**. Total synthesis of **1aa**/**1ab** was completed from the obtained hexaene **23aa**/**23ab** in three steps.[5] Specifically, the cyclic acetal of hexaene **23aa** and **23ab** was selectively removed in the presence of acid-sensitive TBS ethers under Kita−Fujioka conditions (TMSOTf and 2,6-lutidine; aqueous workup), leading to **27aa,ab**, respectively.[34] After oxidation of aldehydes **27aa,ab** to the carboxylic acids **28aa,ab** with $NaClO_2$, removal of the two TBS groups with TBAF delivered (14*S*,20*R*)-**1aa** and (14*S*,20*S*)-**1ab**, respectively. The $^1H-^1H$ coupling constants confirmed no geometric isomerization from the (*E*,*Z*)-diene to the more stable (*E*,*E*)-diene under this series of reaction conditions. As shown in Scheme 9, two other stereoisomers of **1aa**, (14*R*,20*R*)-**1ba** and (14*R*,20*S*)-**1bb**, were also synthesized by application of the same 6-step sequence to

Scheme 8. Total Synthesis of (14*S*,20*R*)-1aa and (14*S*,20*S*)-1ab



2ba and **2bb**. Hence, the total synthesis of all the stereoisomers of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid was accomplished. HPLC analysis of DHA-derived natural **1** and the synthetic **1aa,ab,ba,bb** established the absolute structure of natural **1** to be (14*S*,20*R*)-**1aa**.[7,35]

We evaluated the anti-inflammatory activity of synthetic (14*S*,20*R*)-**1aa**, (14*S*,20*S*)-**1ab**, (14*R*,20*R*)-**1ba**, and (14*R*,20*S*)-**1bb** using an in vivo inflammation model (Figure 2).[36] Zymosan A, a glucan from the yeast cell wall, was used to induce acute peritonitis in mice. Intravenous administration of the four compounds at a concentration as low as 1 ng significantly blocked the infiltration of PMN leucocytes at 2 h in the inflamed peritoneal cavity. Importantly, all of the artificial isomers **1ab,ba,bb** displayed the same level of anti-inflammatory activity as the natural form (**1aa**), indicating the inconsequential nature of the stereochemistries of the two hydroxy groups of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-

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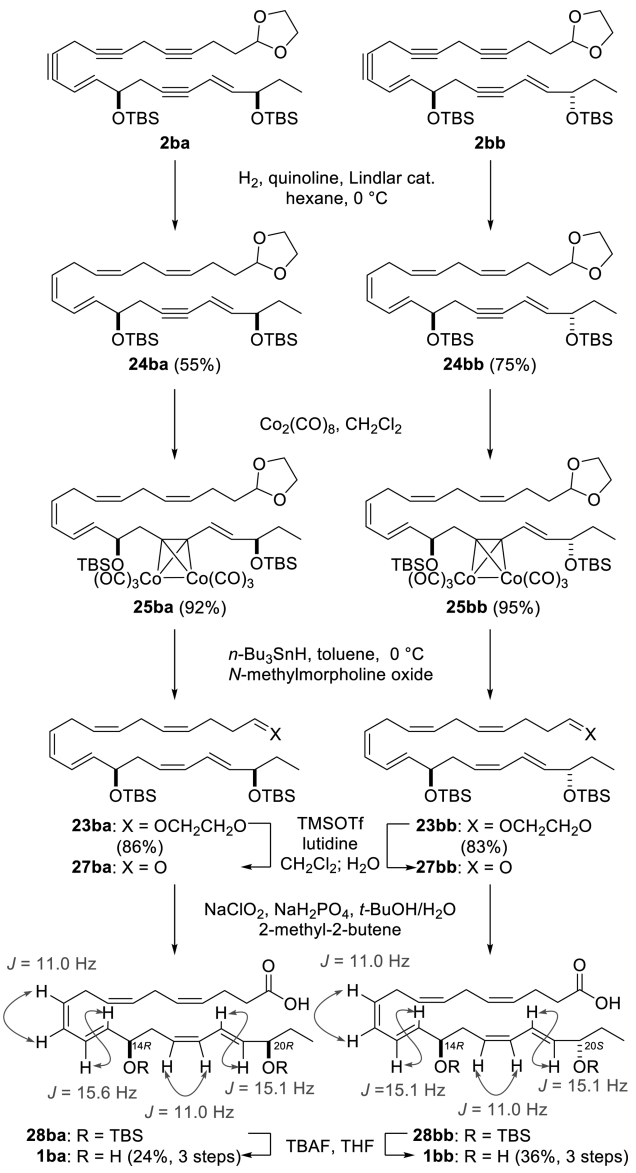
Scheme 9. Total Synthesis of (14*R*,20*R*)-1ba and (14*R*,20*S*)-1bb



4,7,10,12,16,18-docosahexaenoic acid for potent anti-inflammatory activity.

CONCLUSION

We established a unified route to the four stereoisomers of the new lipid mediator **1**, (14*S*,20*R*)-**1aa**, (14*S*,20*S*)-**1ab**, (14*R*,20*R*)-**1ba**, and (14*R*,20*S*)-**1bb**, from the six simple fragments **6**–**11** and iodoform in 16 longest linear steps and 19 overall steps. These total syntheses allowed the absolute structure of the naturally occurring **1** to be determined as **1aa**, and the anti-inflammatory activities of all four stereoisomers were shown to be equipotent for the first time. The key features of the synthesis route include (i) enantioselective reduction of the C20-ketone with chiral 2-butyl-CBS-oxazaborolidines for the synthesis of C16–C22 fragments **5a,b**, (ii) construction of the carbon backbone of **1** by employing two Sonogashira couplings and three S_N2 alkynylations, and (iii) chemoselective formation of the four (*Z*)-alkenes by stepwise reduction using Lindlar reduction of the three alkynes (C4–C5, C7–C8, and

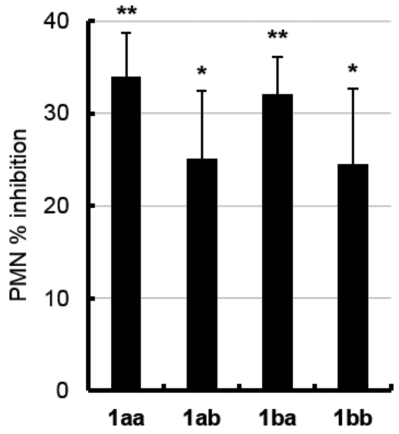


Figure 2. Bioassay of synthetic **1aa,ab,ba,bb**. The compounds (1 ng) were injected intravenously through the tail vein, followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected and the number of PMN leucocytes was counted. Values represent mean ± SE, $n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

C10–C11) and modified Isobe reduction of the remaining C16–C17 alkyne. Construction of the (*Z*)-alkene from the sterically shielded alkyne by combining Co-complexation and reductive decomplexation should have wider application for the chemoselective preparation of various (*Z*)-alkenes beyond this target. Further studies toward functional analysis of **1aa** and the non-natural isomers are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out under an argon atmosphere in dry solvents, unless otherwise noted. THF, CH_2Cl_2, and toluene were purified by a 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. Analytical thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel (spherical, neutral, 40–50 μm; 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 prepacked silica gel 40 μm (45 g (26 × 150 mm) or 120 g (46 × 130 mm)). 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), C_6D_6 for ^{13}C NMR (δ 128.06), 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 follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. High-resolution mass spectra were measured on ESI-TOF and DART-TOF mass spectrometers.

(*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-one (13). A solution of propionyl chloride (1.86 g, 20.1 mmol) in CH_2Cl_2 (30 mL) and a solution of **12** (3.00 g, 16.8 mmol) in CH_2Cl_2 (30 mL) were successively added to a solution of $AlCl_3$ (2.69 g, 20.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h, and then saturated aqueous NH_4Cl (70 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (50 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium-pressure liquid chromatography on silica gel (45 g, pentane to pentane/Et_2O 16/1) to afford a 3.5/1 mixture of bromide **7** and

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chloride **7′** along with pentane and Et_2O (3.05 g), which was used in the next reaction without further purification due to the volatility of **7**.

$Pd(PPh_3)_4$ (528 mg, 0.457 mmol), CuI (174 mg, 0.916 mmol), Et_3N (5.3 mL, 38 mmol), and (trimethylsilyl)acetylene **8** (4.3 mL, 30 mmol) were successively added to a solution of the above 3.5/1 mixture of **7** and **7′** at room temperature. The reaction mixture was stirred at room temperature for 2.5 h. After the reaction mixture was cooled to 0 °C, saturated aqueous NH_4Cl (50 mL) was added. The resultant mixture was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (120 g, pentane to pentane/Et_2O 16/1) to afford **13** (2.74 g, 11.2 mmol, a 5/1.5/1 mixture of ketone **13**, Et_2O, and pentane). The yield of **13** was determined to be 67% over two steps by the ^1H NMR analysis of the mixture. For characterization of **13**, the residual solvents of the above mixture were completely removed: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 2.56 (q, J = 7.3 Hz, 2H), 1.10 (t, J = 7.3 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 137.7, 122.4, 105.5, 101.9, 34.3, 7.8, −0.5 (×3); IR (neat) ν 2962, 2940, 2902, 1692, 1677, 1596, 1252, 1081, 1020 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}OSiNa$ 203.0863 $[M + Na]^+$, found 203.0864.

(*R*,*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol (15a). $BH_3{\cdot}Me_2S$ (1.5 mL, 16 mmol) was added to a solution of (*S*)-2-butyl-CBS-oxazaborolidine **14a** (1.0 M solution in toluene, 14 mL, 14 mmol) in toluene (46 mL) at room temperature. The mixture was stirred at room temperature for 30 min. After the mixture was cooled to −78 °C, a solution of **13** (2.42 g, 7.41 mmol, a 27/53/1 mixture of **13**, pentane and Et_2O) in toluene (23 mL) was added over 35 min. The reaction mixture was stirred at −78 °C for 1 h, and then 0.4 M aqueous HCl (60 mL) was added. The mixture was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (100 and 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), 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 (120 g, hexane to hexane/EtOAc 5/1) to afford **15a** (868 mg, 4.77 mmol) in 64% yield. The enantiopurity of **15a** was determined to be 96% ee by the ^1H NMR analysis of the corresponding MTPA ester: colorless oil; $[\alpha]_D^{28}$ −4.2 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (dd, J = 16.0, 6.0 Hz, 1H), 5.73 (dd, J = 16.0, 1.4 Hz, 1H), 4.09 (m, 1H), 1.57 (qd, J = 7.3, 6.0 Hz, 2H), 1.46 (d, J = 4.6 Hz, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 110.0, 103.1, 95.1, 73.5, 29.8, 9.5, −0.12 (×3); IR (neat) ν 3357, 2962, 2935, 2877, 2155, 2130, 1457, 1250 cm^{-1}; HRMS (DART) calcd for $C_{10}H_{19}OSi$ 183.1200 $[M + H]^+$, found 183.1208.

(*S*,*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol (15b). According to the synthetic procedure of **15a**, **15b** (965 mg, 5.30 mmol) was synthesized from **13** (2.82 g, 8.65 mmol, a 27/53/1 mixture of **13**, pentane, and Et_2O) in 65% yield by using (*R*)-2-butyl-CBS-oxazaborolidine **14b** (1.0 M solution in toluene, 16.3 mL, 16.3 mmol) and $BH_3{\cdot}Me_2S$ (1.8 mL, 18 mmol) in toluene (83 mL). Purification was performed twice by medium-pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 6/1; 45 g, hexane to hexane/EtOAc 6/1). The enantiopurity of **15b** was determined to be 96% ee by the ^1H NMR analysis of the corresponding MTPA ester: colorless oil; $[\alpha]_D^{30}$ +4.3 (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}OSi$: C, 65.87; H, 9.95. Found: C, 66.04; H, 9.71. The other analytical data of **15b** were identical with those of **15a**.

C16−C22 Fragment 5a. TBSCl (1.43 g, 9.49 mmol) was added to a solution of alcohol **15a** (864 mg, 4.75 mmol) and imidazole (1.29 g, 20.0 mmol) in DMF (47 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h, and then H_2O (100 mL) was added. The resultant solution was extracted with Et_2O (60 and 40 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 to afford the crude TBS ether **16a**, which was used in the next reaction without further purification.

K_2CO_3 (980 mg, 7.10 mmol) was added to a solution of the above crude TBS ether **16a** in MeOH (45 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. After the reaction mixture was cooled to 0 °C, Et_2O (50 mL) and saturated aqueous NH_4Cl (60 mL) were successively added. The resultant mixture was extracted with Et_2O (100 and 50 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 three times by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 25/1; 30 g, hexane/EtOAc 100/1 to 50/1; 30 g, hexane to hexane/EtOAc 100/1) to afford C16−C22 fragment **5a** (718 mg, 3.21 mmol) in 68% over two steps: colorless oil; $[\alpha]_D^{24}$ +19 (*c* 0.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, J = 16.0, 6.0 Hz, 1H), 5.65 (ddd, J = 16.0, 2.3, 1.8 Hz, 1H), 4.12 (dtd, J = 6.0, 6.0, 1.8 Hz, 1H), 2.86 (d, J = 2.3 Hz, 1H), 1.52 (m, 2H), 0.90 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 107.6, 82.2, 77.2, 73.3, 30.5, 25.8 (×3), 18.2, 9.2, −4.6, −4.9; IR (neat) ν 3427, 2956, 2930, 2858, 2221, 1471, 1463, 1362, 1255 cm^{-1}. Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.42; H, 10.48.

C16−C22 Fragment 5b. According to the synthetic procedure of **5a**, **5b** (1.73 g, 7.72 mmol) was synthesized from **15b** (1.71 g, 9.40 mmol) in 82% yield over two steps by using TBSCl (2.84 g, 18.8 mmol) and imidazole (2.55 g, 37.5 mmol) in DMF (100 mL) for the first step and K_2CO_3 (1.94 g, 14.1 mmol) in MeOH (100 mL) for the second. Purification was performed twice by medium-pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 30/1 to 20/1; 45 g, hexane to hexane/EtOAc 30/1 to 20/1): colorless oil; $[\alpha]_D^{24}$ −18 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.39; H, 10.48. The other analytical data of **5b** were identical with those of **5a**.

(*S*)-MTPA Ester 17a. (*R*)-MTPACl (12 μL, 64 μmol) was added to a solution of **15a** (3.0 mg, 16 μmol), Et_3N (16 μL, 0.12 mmol), and DMAP (10 mg, 82 μmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min, and then H_2O (5 mL) was added. The resultant mixture was extracted with EtOAc (5 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 (1 g, hexane/EtOAc 20/1) to afford (*S*)-MTPA ester **17a** (4.9 mg, 13 μmol) in 81% yield: colorless oil; ^1H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.42−7.36 (m, 3H), 6.02 (dd, J = 16.0, 7.3 Hz, 1H), 5.70 (d, J = 16.0 Hz, 1H), 5.40 (dt, J = 7.3, 6.4 Hz, 1H), 3.55 (s, 3H), 1.80−1.67 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.19 (s, 9H).

(*R*)-MTPA Ester 17a′. According to the synthetic procedure of **17a**, (*R*)-MTPA ester **17a′** (4.1 mg, 11 μmol) was synthesized from **15a** (2.6 mg, 14 μmol) in 79% yield by using (*S*)-MTPACl (5.5 μL, 29 μmol), Et_3N (10 μL, 0.12 mmol), and DMAP (4.4 mg, 36 μmol) in CH_2Cl_2 (0.7 mL). The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 20/1): colorless oil; ^1H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.42−7.38 (m, 3H), 6.10 (dd, J = 16.0, 6.8 Hz, 1H), 5.79 (d, J = 16.0 Hz, 1H), 5.42 (td, J = 6.8, 6.8 Hz, 1H), 3.54 (s, 3H), 1.75−1.55 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H), 0.19 (9H, s).

Alcohol 18aa. *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) was added to a solution of C16−C22 fragment **5a** (714 mg, 3.19 mmol) in THF (25 mL) at −78 °C over 10 min. The mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for 30 min. After the mixture was cooled to −78 °C, $BF_3{\cdot}OEt_2$ (0.36 mL, 2.9 mmol) and a solution of glycidol derivative **6a** (503 mg, 2.68 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at −78 °C for 1 h and warmed to −40 °C over 3 h, and then saturated aqueous NH_4Cl (30 mL) was added. The resultant mixture was extracted with Et_2O (30 mL × 3), 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 twice by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1) and flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford alcohol **18aa** (707 mg,

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1.71 mmol) in 64% yield: colorless oil; $[\alpha]_D^{28}$ +31 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.61 (dtd, *J* = 16.0, 1.8, 1.8 Hz, 1H), 4.08 (dtd, *J* = 6.0, 6.0, 1.8 Hz, 1H), 3.81 (m, 1H), 3.72 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.62 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.60−2.50 (m, 2H), 1.50 (qd, *J* = 7.8, 6.0 Hz, 2H), 0.97 (t, *J* = 8.2 Hz, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.8 Hz, 3H), 0.63 (q, *J* = 8.2 H, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 108.7, 85.8, 80.8, 73.6, 70.4, 65.4, 30.7, 25.8 (×3), 24.1, 18.2, 9.3, 6.7 (×3), 4.3 (×3), −4.6, −4.9; IR (neat) ν 3566, 2956, 2926, 2852, 1956, 1478, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2726.

Alcohol 18ab. According to the synthetic procedure of **18aa**, **18ab** (791 mg, 1.92 mmol) was synthesized from C16−C22 fragment **5b** (833 mg, 3.72 mmol) and glycidol derivative **6a** (596 mg, 3.17 mmol) in 61% yield by using *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol) and $BF_3{\cdot}OEt_2$ (0.41 mL, 3.3 mmol) in THF (31 mL). Purification was performed by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ −5.9 (*c* 0.98, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2716. The other analytical data of **18ab** were identical with those of **18ba**.

Alcohol 18ba. According to the synthetic procedure of **18aa**, **18ba** (760 mg, 1.84 mmol) was synthesized from C16−C22 fragment **5a** (610 mg, 2.72 mmol) and glycidol derivative **6b** (436 mg, 2.32 mmol) in 79% yield by using *n*-BuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.4 mmol) in THF (26 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{30}$ +6.2 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.61 (dtd, *J* = 16.0, 2.3, 1.4 Hz, 1H), 4.08 (dtd, *J* = 6.0, 5.5, 1.4 Hz, 1H), 3.81 (m, 1H), 3.72 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.60−2.50 (m, 2H), 1.50 (qd, *J* = 7.3, 5.5 Hz, 2H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 108.7, 85.8, 80.8, 73.6, 70.4, 65.3, 30.7, 25.8 (×3), 24.1, 18.2, 9.3, 6.7 (×3), 4.3 (×3), −4.5, −4.9; IR (neat) ν 3429, 2956, 2931, 2877, 1463, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2744.

Alcohol 18bb. According to the synthetic procedure of **18aa**, **18bb** (777 mg, 1.88 mmol) was synthesized from C16−C22 fragment **5b** (867 mg, 3.87 mmol) and glycidol derivative **6b** (624 mg, 3.32 mmol) in 57% yield by using *n*-BuLi (1.6 M in hexane, 2.6 mL, 4.2 mmol) and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.5 mmol) in THF (37 mL). Purification was performed by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{24}$ −32 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2713. The other analytical data of **18bb** were identical with those of **18aa**.

Alcohol 19aa. TBSOTf (0.43 mL, 1.9 mmol) was added to a solution of alcohol **18aa** (704 mg, 1.70 mmol) and Et_3N (0.60 mL, 4.3 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 and 20 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 flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford the crude TBS ether, which was used in the next reaction without further purification.

PPTS (37 mg, 0.15 mmol) was added to a solution of the above crude TBS ether in a mixture of MeOH (15 mL) and THF (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min. After the reaction mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 and 20 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified three times by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 20/1) to afford TBS ether **19aa** (463 mg, 1.12 mmol) in 66% over two steps: colorless oil; $[\alpha]_D^{21}$ +21 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.60 (dtd, *J* = 16.0, 1.8, 1.4 Hz, 1H), 4.07 (tdd, *J* = 6.4, 6.0, 1.4 Hz, 1H), 3.91 (m, 1H), 3.68 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.58 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.53 (ddd, *J* = 17.0, 6.9, 1.8 Hz, 1H), 2.42 (ddd, *J* = 17.0, 6.4, 1.8 Hz, 1H), 1.50 (qd, *J* = 7.3, 6.4 Hz, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 109.1, 86.7, 81.0, 74.0, 72.0, 66.2, 31.0, 26.2 (×3), 26.1 (×3), 25.1, 18.5, 18.4, 9.6, −4.21, −4.24, −4.5, −4.6; IR (neat) ν 3449, 2955, 2929, 2857, 1471, 1461, 1362, 1255, 1113 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2709.

Alcohol 19ab. According to the synthetic procedure of **19aa**, **19ab** (453 mg, 1.10 mmol) was synthesized from alcohol **18ab** (780 mg, 1.89 mmol) in 58% yield over two steps by using Et_3N (0.66 mL, 4.7 mmol) and TBSOTf (0.48 mL, 2.1 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (40 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 20/1) for the first step, and on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{25}$ −17 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2721. The other analytical data of **19ab** were identical with those of **19ba**.

Alcohol 19ba. According to the synthetic procedure of **19aa**, **19ba** (427 mg, 1.04 mmol) was synthesized from alcohol **18ba** (676 mg, 1.64 mmol) in 63% yield over two steps by using Et_3N (0.58 mL, 4.2 mmol) and TBSOTf (0.42 mL, 1.8 mmol) in CH_2Cl_2 (16 mL) for the first step, and PPTS (37 mg, 0.15 mmol) in a mixture of MeOH (15 mL) and THF (2.5 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step, and twice on silica gel (30 g, hexane to hexane/EtOAc 9/1; 30 g, hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{31}$ +17 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.60 (ddt, *J* = 16.0, 2.3, 1.4 Hz, 1H), 4.07 (tdd, *J* = 6.0, 6.0, 1.4 Hz, 1H), 3.91 (m, 1H), 3.68 (ddd, *J* = 11.4, 6.0, 3.7 Hz, 1H), 3.58 (ddd, *J* = 11.4, 6.0, 5.0 Hz, 1H), 2.53 (ddd, *J* = 16.9, 7.3, 2.3 Hz, 1H), 2.47 (ddd, *J* = 16.9, 6.0, 2.3 Hz, 1H), 1.87 (t, *J* = 6.0 Hz, 1H), 1.50 (qd, *J* = 7.8, 6.0 Hz, 2H), 0.904 (s, 9H), 0.895 (s, 9H), 0.86 (t, *J* = 7.8 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.6, −4.5, 9.3, 18.1, 18.2, 24.8, 25.77 (×3), 25.84 (×3), 30.7, 65.9, 71.7, 73.6, 80.7, 86.4, 108.8, 145.5; IR (neat) ν 3434, 2956, 2929, 2857, 2221, 1634, 1472, 1464, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2744.

Alcohol 19bb. According to the synthetic procedure of **19aa**, **19bb** (480 mg, 1.16 mmol) was synthesized from alcohol **18bb** (766 mg, 1.86 mmol) in 62% yield over two steps by using Et_3N (0.65 mL, 4.7 mmol) and TBSOTf (0.47 mL, 2.0 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (41 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step and twice on silica gel (30 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{23}$ −20 (*c* 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2738. The other analytical data of **19bb** were identical with those of **19aa**.

Aldehyde 20aa. Dess−Martin periodinane (693 mg, 1.63 mmol) was added to a suspension mixture of alcohol **19aa** (449 mg, 1.09 mmol) and $NaHCO_3$ (887 mg, 10.6 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 5 h, and then H_2O (50 mL) was added. The resultant mixture was extracted with Et_2O (50 and 30 mL × 2), 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 flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1) to afford aldehyde **20aa** (343 mg, 0.835 mmol) in 77% yield: colorless oil; $[\alpha]_D^{29}$ −3.4 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.4 Hz, 1H), 6.04 (dd, *J* = 16.0, 5.5 Hz, 1H), 5.60 (br d, *J* = 16.0 Hz, 1H), 4.13 (ddd, *J* = 7.8, 5.0, 1.4 Hz, 1H), 4.07

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(td, J = 6.0, 5.5 Hz, 1H), 2.71 (ddd, J = 16.9, 5.0, 1.8 Hz, 1H), 2.57 (ddd, J = 16.9, 7.8, 1.8 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.93 (s, 9H), 0.89 (s, 9H), 0.86 (t, J = 7.3 Hz, 3H), 0.13 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 145.9, 108.6, 85.0, 81.2, 76.2, 73.6, 30.7, 25.8 (×3), 25.7 (×3), 24.1, 18.23, 18.22, 9.3, −4.6, −4.78, −4.82, −4.9; IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2819.

Aldehyde 20ab. According to the synthetic procedure of **20aa**, **20ab** (393 mg, 0.956 mmol) was synthesized from alcohol **19ab** (437 mg, 1.06 mmol) in 90% yield by using $NaHCO_3$ (861 mg, 10.3 mmol) and Dess−Martin periodinane (677 mg, 1.60 mmol) in CH_2Cl_2 (22 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ −52 (c 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2832. The other analytical data of **20ab** were identical with those of **20ba.**

Aldehyde 20ba. According to the synthetic procedure of **20aa**, **20ba** (352 mg, 0.856 mmol) was synthesized from alcohol **19ba** (418 mg, 1.01 mmol) in 85% yield by using $NaHCO_3$ (818 mg, 10.8 mmol) and Dess−Martin periodinane (645 mg, 1.52 mmol) in CH_2Cl_2 (21 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ +47 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 1.0 Hz, 1H), 6.04 (dd, J = 16.0, 6.0 Hz, 1H), 5.60 (dd, J = 16.0, 1.8 Hz, 1H), 4.13 (ddd, J = 7.8, 5.0, 1.0 Hz, 1H), 4.08 (td, J = 6.0, 6.0 Hz, 1H), 2.71 (ddd, J = 17.0, 5.0, 1.8 Hz, 1H), 2.57 (ddd, J = 17.0, 7.8, 1.8 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.86 (t, J = 7.3 Hz, 3H), 0.136 (s, 3H), 0.132 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 146.0, 108.6, 85.0, 81.2, 76.2, 73.6, 30.7, 25.8 (×3), 25.7 (×3), 24.1, 18.2 (×2), 9.3, −4.6, −4.78, −4.82, −4.9; IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 1117 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2851.

Aldehyde 20bb. According to the synthetic procedure of **20aa**, **20bb** (378 mg, 0.920 mmol) was synthesized from alcohol **19bb** (472 mg, 1.15 mmol) in 80% yield by using $NaHCO_3$ (904 mg, 10.8 mmol) and Dess-Martin periodinane (1.20 g, 2.83 mmol) in CH_2Cl_2 (24 mL). Purification was performed twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1; 30 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{22}$ +12 (c 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2825. The other analytical data of **20bb** were identical with those of **20aa**.

C12−C22 Fragment 3aa. Iodoform (644 mg, 1.63 mmol) and a solution of aldehyde **20aa** (334 mg, 0.813 mmol) in 1,4-dioxane (13.5 mL) were successively added to a suspension of $CrCl_2$ (600 mg, 4.88 mmol) in THF (0.98 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (40 mL) and H_2O (20 mL) were successively added. The resultant mixture was extracted with Et_2O (50 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 twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1; 40 g, hexane/EtOAc 20/1) to afford **3aa** (297 mg, 0.555 mmol) in 68% yield: colorless oil; $[\alpha]_D^{31}$ +47 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dd, J = 14.8, 5.5 Hz, 1H), 6.33 (dd, J = 14.8, 1.4 Hz, 1H), 6.03 (dd, J = 16.0, 6.0 Hz, 1H), 5.61 (ddt, J = 16.0, 2.3, 1.8 Hz, 1H), 4.24 (td, J = 6.9, 5.5, 1.4 Hz, 1H), 4.08 (td, J = 6.0, 6.0 Hz, 1H), 2.49 (ddd, J = 16.9, 6.9, 2.3 Hz, 1H), 2.42 (ddd, J = 16.9, 6.9, 2.3 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.899 (s, 9H), 0.896 (s, 9H), 0.87 (t, J = 7.8 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.7, 108.8, 86.1, 81.1, 76.7, 74.0, 73.6, 30.7, 28.8, 25.9 (×3), 25.7 (×3), 18.22, 18.19, 9.3, −4.5, −4.7, −4.86, −4.89; IR (neat) ν 2956, 2929, 2857, 1607, 1471, 1463, 1362, 1255, 1092 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1733.

C12−C22 Fragment 3ab. According to the synthetic procedure of **3aa**, **3ab** (218 mg, 0.407 mmol) was synthesized from aldehyde **20ab** (384 mg, 0.934 mmol) in 44% yield by using iodoform (739 mg, 1.88 mmol) and $CrCl_2$ (687 mg, 5.58 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15.5 mL). Purification was performed three times by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1; 30 g, hexane to hexane/EtOAc 20/1; 30 g, hexane/CH_2Cl_2 100/1 to 20/1): colorless oil; $[\alpha]_D^{23}$ +25 (c 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1728. The other analytical data of **3ab** were identical with those of **3ba**.

C12−C22 Fragment 3ba. According to the synthetic procedure of **3aa**, **3ba** (270 mg, 0.505 mmol) was synthesized from aldehyde **20ba** (342 mg, 0.832 mmol) in 61% yield by using iodoform (657 mg, 1.67 mmol) and $CrCl_2$ (615 mg, 5.00 mmol) in a mixture of THF (1.0 mL) and 1,4-dioxane (14 mL). Purification was performed three times by flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ −16 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (ddd, J = 14.6, 5.5 Hz, 1H), 6.33 (dd, J = 14.6, 1.4 Hz, 1H), 6.03 (dd, J = 16.0, 6.0 Hz, 1H), 5.61 (dd, J = 16.0, 1.4 Hz, 1H), 4.24 (td, J = 6.9, 5.5 Hz, 1H), 4.08 (dt, J = 6.0, 6.0 Hz, 1H), 2.49 (ddd, J = 16.9, 6.9, 1.8 Hz, 1H), 2.42 (ddd, J = 16.9, 6.9, 1.8 Hz, 1H), 1.50 (qd, J = 7.8, 6.0 Hz, 2H), 0.899 (s, 9H), 0.896 (s, 9H), 0.87 (t, J = 7.8 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.7, 108.8, 86.1, 81.0, 76.7, 74.0, 73.7, 30.7, 28.8, 25.9 (×3), 25.7 (×3), 18.23, 18.19, 9.3, −4.5, −4.7, −4.86, −4.89; IR (neat) ν 2956, 2929, 2857, 1607, 1463, 1362, 1255, 1090 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1754.

C12−C22 Fragment 3bb. According to the synthetic procedure of **3aa**, **3bb** (213 mg, 0.391 mmol) was synthesized from aldehyde **20bb** (370 mg, 0.900 mmol) in 43% yield by using iodoform (571 mg, 1.45 mmol) and $CrCl_2$ (657 mg, 5.34 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/CH_2Cl_2 20/1 to 12/1): colorless oil; $[\alpha]_D^{22}$ −50 (c 0.77, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1719. The other analytical data of **3bb** were identical with those of **3aa.**

Triyne 4. A mixture of CuI (833 mg, 4.37 mmol), NaI (650 mg, 4.34 mmol), and Cs_2CO_3 (1.41 g, 4.32 mmol) was dried at 95 °C in vacuo. After the mixture was cooled to 0 °C, a solution of alcohol **9** (548 mg, 4.35 mmol) in DMF (4.0 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **10** (1.18 g, 4.91 mmol) in DMF (4.8 mL) was added. The reaction mixture was warmed to room temperature and stirred for 16 h, and then saturated aqueous NH_4Cl (20 mL) was added. The resultant solution was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (30 and 20 mL × 2). 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 3/2) to afford the crude diyne **21**, which was used in the next reaction without further purification.

DIPHOS (1.48 g, 3.72 mmol) and CBr_4 (827 mg, 2.49 mmol) were successively added to a solution of the above crude **21** in CH_2Cl_2 (12 mL) to 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then was directly subjected to medium-pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 8/1) to afford bromide **22**, which was immediately used in the next reaction.

CuCl (181 mg, 1.83 mmol) was dried at 90 °C in vacuo, and then THF (25 mL) was added. Ethynylmagnesium bromide (**11′**; 0.5 M in THF, 27 mL, 14 mmol) was added to the suspension at room temperature. The mixture was stirred for 10 min at room temperature, and then a solution of the above bromide **22** in THF (30 mL) was added. The reaction mixture was stirred at room temperature for 14 h, and then saturated aqueous NH_4Cl (50 mL) was added. The resultant solution was filtered through a pad of Celite, and the filtrate was extracted with EtOAc (50 and 30 mL). 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 flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1 to 9/1) to afford triyne **4** (228 mg, 1.04 mmol) in 24% yield over three steps. Triyne **4** was immediately used in the next reaction due to its

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instability in air: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (t, J = 4.6 Hz, 1H), 4.00−3.91 (m, 2H), 3.91−3.82 (m, 2H), 3.17 (dt, J = 2.7, 2.3 Hz, 2H), 3.13 (tt, J = 2.3, 2.3 Hz, 2H), 2.30 (tt, J = 7.2, 2.3 Hz, 2H), 2.06 (t, J = 2.7 Hz, 1H), 1.85 (td, J = 7.3, 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.2, 79.7, 78.1, 75.5, 73.9, 73.4, 68.7, 64.9 (×2), 32.9, 13.6, 9.7, 9.6; IR (neat) ν 3287, 2887, 1413, 1317, 1138, 1038 cm^{-1}.

Tetrayne 2aa. $Pd(PPh_3)_4$ (92 mg, 80 μmol), CuI (32 mg, 0.17 mmol), a solution of C12−C22 fragment **3aa** (278 mg, 0.520 mmol) in benzene (4.5 mL), and piperidine (0.16 mL, 1.6 mmol) were successively added to a solution of **4** (157 mg, 0.777 mmol) in benzene (14 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (10 mL) and saturated aqueous NH_4Cl (40 mL) were successively added. The resultant mixture was extracted with Et_2O (30 and 10 mL), and the 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 (30 g, hexane/EtOAc 15/1) to afford tetrayne **2aa** (223 mg, 0.366 mmol) in 70% yield. Tetrayne **2aa** was immediately used in the next reaction due to its instability in air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 6.20 (dd, J = 15.6, 5.5 Hz, 1H), 6.16 (dd, J = 15.6, 5.5 Hz, 1H), 5.87−5.78 (m, 2H), 4.87 (t, J = 5.0 Hz, 1H), 4.16 (td, J = 6.0, 5.5 Hz, 1H), 3.91 (td, J = 6.0, 5.5 Hz, 1H), 3.47−3.38 (m, 2H), 3.33−3.25 (m, 2H), 2.94 (s, 2H), 2.85 (br s, 2H), 2.41 (dd, J = 16.0, 6.9 Hz, 1H), 2.30 (dd, J = 16.0, 6.4 Hz, 1H), 2.28 (br t, J = 7.8 Hz, 2H), 1.86 (td, J = 7.8, 5.0 Hz, 2H), 1.42 (qd, J = 7.3, 6.0 Hz, 2H), 0.97 (s, 9H), 0.95 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.6, 144.8, 110.1, 109.9, 103.4, 87.5, 85.2, 81.2, 80.1, 79.1, 75.8, 74.5, 74.4, 74.1, 71.9, 64.8 (×2), 33.6, 31.1, 29.5, 26.1 (×3), 26.0 (×3), 18.43, 18.41, 14.0, 10.5, 9.9, 9.5, −4.3, −4.5, −4.71, −4.73; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 [M + Na]$^+$, found 631.3587.

Tetrayne 2ab. According to the synthetic procedure of **2aa**, **2ab** (175 mg, 0.287 mmol) was synthesized from **3ab** (218 mg, 0.407 mmol) and **4** (98 mg, 0.49 mmol) in 71% yield by using $Pd(PPh_3)_4$ (69 mg, 60 μmol), CuI (23 mg, 0.12 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 6.20 (dd, J = 15.1, 5.0 Hz, 1H), 6.16 (dd, J = 15.6, 5.5 Hz, 1H), 5.88−5.78 (m, 2H), 4.87 (t, J = 5.0 Hz, 1H), 4.16 (dt, J = 6.0, 6.0 Hz, 1H), 3.92 (dt, J = 6.0, 6.0 Hz, 1H), 3.47−3.38 (m, 2H), 3.33−3.27 (m, 2H), 2.94 (d, J = 2.3 Hz, 2H), 2.85 (tt, J = 2.3, 2.3 Hz, 2H), 2.42 (ddd, J = 16.5, 6.9, 1.8 Hz, 1H), 2.30 (ddd, J = 16.5, 6.0, 1.8 Hz, 1H), 2.28 (tt, J = 7.3, 2.3 Hz, 2H), 1.86 (td, J = 7.3, 5.0 Hz, 2H), 1.41 (qd, J = 7.3, 6.0 Hz, 2H), 0.97 (s, 9H), 0.95 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H) 0.00 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 145.6, 144.8, 110.1, 109.9, 103.4, 87.5, 85.2, 81.2, 80.1, 79.1, 75.8, 74.5, 74.4, 74.1, 71.9, 64.8 (×2), 33.6, 31.1, 29.5, 26.1 (×3), 26.0 (×3), 18.43, 18.42, 14.0, 10.5, 9.9, 9.5, −4.3, −4.5, −4.72, −4.74.

Tetrayne 2ba. According to the synthetic procedure of **2aa**, **2ba** (174 mg, 0.286 mmol) was synthesized from **3ba** (218 mg, 0.407 mmol) and **4** (127 mg, 0.629 mmol) in 70% yield by using $Pd(PPh_3)_4$ (74 mg, 64 μmol), CuI (23 mg, 0.12 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14.5 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 15/1): pale yellow oil; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 [M + Na]$^+$, found 631.3613. The ^{1}H NMR spectrum of **2ba** was identical with that of **2ab**.

Tetrayne 2bb. According to the synthetic procedure of **2aa**, **2bb** (144 mg, 0.236 mmol) was synthesized from **3bb** (203 mg, 0.380 mmol) and **4** (93 mg, 0.460 mmol) in 62% yield by using $Pd(PPh_3)_4$ (65 mg, 56 μmol), CuI (22 mg, 0.12 mmol), and piperidine (0.12 mL, 1.20 mmol) in benzene (13 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil. The ^{1}H NMR spectrum of **2bb** was identical with that of **2aa**.

Alkyne 24aa. A suspension of tetrayne **2aa** (32.4 mg, 53.2 μmol), quinoline (75 μL, 0.64 mmol), and Lindlar catalyst (65 mg) in hexane (3.0 mL) was stirred 0 °C for 1 h under an H_2 atmosphere (1 atm). Then Lindlar catalyst (39 mg) was added. The reaction mixture was stirred at 0 °C for a further 40 min under an H_2 atmosphere and was filtered through a pad of Celite with hexane. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1) and twice on Chromatorex-ACD (10 g, hexane/EtOAc 500/1 to 300/1; 8 g, hexane/EtOAc 500/1 to 200/1) to afford alkyne **24aa** (18.1 mg, 29.4 μmol) in 55% yield: colorless oil; $[\alpha]_D^{27}$ +41 (c 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.74 (dd, J = 15.6, 11.4 Hz, 1H), 6.19 (dd, J = 15.6, 6.0 Hz, 1H), 6.02 (dd, J = 11.4, 11.4 Hz, 1H), 5.86 (ddt, J = 15.6, 1.4, 1.4 Hz, 1H), 5.77 (dd, J = 15.6, 6.0 Hz, 1H), 5.50−5.47 (m, 5H), 4.84 (t, J = 4.6 Hz, 1H), 4.38 (dt, J = 6.4, 6.0 Hz, 1H), 3.93 (dt, J = 6.0, 6.0 Hz, 1H), 3.60−3.52 (m, 2H), 3.42−3.35 (m, 2H), 2.99 (t, J = 6.4 Hz, 2H), 2.87 (m, 2H), 2.59 (ddd, J = 16.9, 7.3, 2.3 Hz, 1H), 2.45 (ddd, J = 16.9, 5.9, 2.3 Hz, 1H), 2.31 (m, 2H), 1.81 (m, 2H), 1.43 (m, 2H), 1.04 (s, 9H), 0.97 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.6, 129.9, 129.2, 128.6, 128.3, 128.0, 127.6, 124.7, 109.0, 104.1, 87.3, 80.4, 73.7, 72.0, 64.9 (×2), 33.7, 30.7, 29.6, 26.0, 25.83 (×3), 25.80 (×3), 25.5, 21.9, 18.3, 18.2, 9.3, −4.5, −4.6, −4.8, −4.9; IR (neat) ν 2961, 2926, 2855, 1733, 1457, 1260, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4094.

Alkyne 24ab. According to the synthetic procedure of **24aa**, **24ab** (87.8 mg, 0.143 mmol) was synthesized from **2ab** (86.9 mg, 0.143 mmol) in 100% yield by using Lindlar catalyst (180 mg) and quinoline (0.20 mL, 1.4 mmol) in hexane (8.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 30/1): colorless oil; $[\alpha]_D^{19}$ +16 (c 1.4, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4083. The other analytical data of **24ab** were identical with those of **24ba**.

Alkyne 24ba. According to the synthetic procedure of **24aa**, **24ba** (34.0 mg, 55.3 μmol) was synthesized from **2ba** (61.7 mg, 0.101 mmol) in 55% yield by using Lindlar catalyst (500 mg) and quinoline (0.14 mL, 1.2 mmol) in hexane (6.2 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 30/1 to 20/1) and three times on Chromatorex-ACD (20 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{24}$ −20 (c 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.75 (dd, J = 15.6, 11.4 Hz, 1H), 6.19 (dd, J = 15.6, 6.0 Hz, 1H), 6.02 (dd, J = 11.4, 11.4 Hz, 1H), 5.86 (ddt, J = 15.6, 1.4, 1.4 Hz, 1H), 5.77 (dd, J = 15.6, 6.0 Hz, 1H), 5.50−5.47 (m, 5H), 4.84 (t, J = 4.6 Hz, 1H), 4.38 (dt, J = 6.4, 6.0 Hz, 1H), 3.93 (dt, J = 6.0, 6.0 Hz, 1H), 3.60−3.52 (m, 2H), 3.42−3.35 (m, 2H), 3.00 (t, J = 6.4 Hz, 2H), 2.87 (m, 2H), 2.59 (ddd, J = 16.9, 7.3, 2.3 Hz, 1H), 2.45 (ddd, J = 16.9, 5.9, 2.3 Hz, 1H), 2.31 (m, 2H), 1.81 (m, 2H), 1.43 (m, 2H), 1.04 (s, 9H), 0.97 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H), 0.17 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.6, 129.9, 129.2, 128.6, 128.3, 128.0, 127.7, 124.7, 109.0, 104.1, 87.3, 80.4, 73.7, 72.0, 64.9 (×2), 33.7, 30.7, 29.6, 26.0, 25.84 (×3), 25.81 (×3), 25.6, 21.9, 18.3, 18.2, 9.3, −4.5, −4.6, −4.8, −4.9; IR (neat) ν 2956, 2928, 2856, 1472, 1255, 1136 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4080.

Allkyne 24bb. According to the synthetic procedure of **24aa**, **24bb** (51.7 mg, 84.1 μmol) was synthesized from **2bb** (68.4 mg, 0.112 mmol) in 75% yield by using Lindlar catalyst (173 mg) and quinoline (0.16 mL, 1.4 mmol) in hexane (7.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1) and twice on Chromatorex-ACD (20 g, hexane/EtOAc 500/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{21}$ −43 (c 0.69, $CHCl_3$).. The other analytical data of **24bb** were identical with those of **24aa**.

Complex 25aa. $Co_2(CO)_8$ (69 mg, 0.20 mmol) was added to a solution of **24aa** (31.1 mg, 50.5 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1) to afford **25aa** (42.2 mg, 46.8 mol) in 93% yield: brown oil; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 15.6 Hz, 1H), 6.58 (dd, J = 15.6, 11.5 Hz, 1H), 6.00 (dd, J = 11.5, 11.5 Hz, 1H), 5.99 (dd, J = 15.6, 6.0 Hz, 1H), 5.74 (dd, J = 15.6, 6.0 Hz, 1H), 5.47−5.30 (m, 5H), 4.87 (t, J = 4.6 Hz, 1H), 4.44 (td, J = 6.0, 5.0 Hz, 1H), 4.13 (td, J = 6.4, 6.0 Hz, 1H), 4.01−3.91 (m, 2H), 3.90−3.80 (m, 2H), 3.26−3.15 (m, 2H), 3.00−2.89 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.20 (td, J = 7.3, 7.3 Hz, 2H), 1.72 (m, 2H), 1.54 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.89 (t, J = 7.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.3, 130.5, 129.2, 128.7, 128.3, 128.0, 127.6, 126.4, 125.9, 104.1, 93.8, 74.4, 73.6, 64.9 (×2), 44.0, 33.7, 31.0, 26.0, 25.9 (×3), 25.8 (×3), 25.5, 21.9, 18.34, 18.26, 9.6, −4.46, 4.54, −4.8, some of the ^{13}C peaks were missing due to broadening of the spectrum; IR (neat) ν 2956, 2930, 2858, 2088, 2048, 2018, 1255, 1061 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2457.

Complex 25ab. According to the synthetic procedure of **25aa**, **25ab** (80.2 mg, 89.1 μmol) was synthesized from **24ab** (54.2 mg, 88.1 μmol) in 99% yield by using $Co_2(CO)_8$ (119 mg, 0.348 mmol) in CH_2Cl_2 (6.0 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2507. The ^{1}H NMR spectrum of **25ab** was identical with that of cobalt complex **25ba**.

Complex 25ba. According to the synthetic procedure of **25aa**, **25ba** (41.3 mg, 45.9 μmol) was synthesized from **24ba** (30.5 mg, 49.6 μmol) in 92% yield by using $Co_2(CO)_8$ (69 mg, 0.20 mmol) in CH_2Cl_2 (4.4 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 20/1): brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 15.6 Hz, 1H), 6.59 (dd, J = 15.6, 11.5 Hz, 1H), 6.00 (dd, J = 11.5, 11.5 Hz, 1H), 5.99 (dd, J = 15.6, 6.0 Hz, 1H), 5.75 (dd, J = 15.6, 6.0 Hz, 1H), 5.47−5.30 (m, 5H), 4.87 (t, J = 4.6 Hz, 1H), 4.44 (td, J = 6.0, 5.0 Hz, 1H), 4.13 (td, J = 6.4, 6.0 Hz, 1H), 4.01−3.91 (m, 2H), 3.90−3.80 (m, 2H), 3.26−3.15 (m, 2H), 3.00−2.89 (m, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.20 (td, J = 7.3, 7.3 Hz, 2H), 1.72 (m, 2H), 1.54 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.88 (t, J = 7.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 140.5, 135.3, 130.4, 129.2, 128.7, 128.3, 128.0, 127.6, 126.4, 125.8, 104.1, 93.7, 91.8, 74.3, 73.5, 64.9 (×2), 44.0, 33.7, 31.0, 26.0, 25.9 (×3), 25.8 (×3), 25.5, 21.9, 18.33, 18.26, 9.6, −4.5, −4.6, −4.78, −4.80, some of the ^{13}C peaks were missing due to broadening of the spectrum; IR (neat) ν 2955, 2929, 2857, 2088, 2048, 2018, 1472, 1255, 1062 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2425.

Complex 25bb. According to the synthetic procedure of **25aa**, **25bb** (92.0 mg, 0.102 mmol) was synthesized from **24bb** (66.0 mg, 0.107 mmol) in 95% yield by using $Co_2(CO)_8$ (149 mg, 0.436 mmol) in CH_2Cl_2 (10 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2449. The ^{1}H NMR spectrum of **25bb** was identical with that of complex **25aa**.

Complex 26aa. $Co_2(CO)_8$ (213 mg, 0.623 mmol) was added to a solution of **2aa** (38.3 mg, 62.8 μmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 4 h, and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1) to afford **26aa** (104 mg, 59.4 μmol) in 94% yield: brown oil. Because signals in the ^{1}H NMR spectrum of **26aa** were broad, the formation was confirmed by the MS analysis: LRMS (ESI) calcd for $C_{60}H_{56}Co_8O_{28}Si_2Na$ 1774.7 [M + Na]$^+$, found 1774.7.

Hexaene 23aa. n-Bu_3SnH (0.19 mL, 0.71 mmol) and N-methylmorpholine oxide (55 mg, 0.47 mmol) were successively added to a solution of **25aa** (42.2 mg, 46.9 μmol) in toluene (45 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h under air and was directly subjected to flash column chromatography (a column consecutively packed with silica gel 4 g and 10% (w/w) KF in silica gel 4 g, hexane to hexane/EtOAc 20/1) to afford **23aa** (25.2 mg, 40.8 mmol) in 87% yield: colorless oil; $[\alpha]_D^{27}$ +10 (c 0.93, $CHCl_3$); IR (neat) ν 2955, 2928, 2856, 1471, 1463, 1361, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4233. The ^{1}H NMR spectrum of **23aa** was identical with that of **23bb**.

Hexaene 23ab. According to the synthetic procedure of **23aa**, **23ab** (47.2 mg, 76.6 μmol) was synthesized from **25ab** (80.2 mg, 89.1 μmol) in 86% yield by using n-Bu_3SnH (0.34 mL, 1.3 mmol) and N-methylmorpholine oxide (101 mg, 0.86 mmol) in toluene (45 mL). Purification was performed twice by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1; 8 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{22}$ +21 (c 0.96, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4246. The other analytical data of **23ab** were identical with those of **23ba**.

Hexaene 23ba. According to the synthetic procedure of **23aa**, **23ba** (24.5 mg, 39.7 μmol) was synthesized from **25ba** (41.3 mg, 45.9 μmol) in 86% yield by using n-Bu_3SnH (0.19 mL, 0.71 mmol) and N-methylmorpholine oxide (54 mg, 0.46 mmol) in toluene (40 mL). Purification was performed by flash column chromatography (a column consecutively packed with silica gel 3 g and 10% (w/w) KF in silica gel 1 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{23}$ −24 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 15.6, 11.4 Hz, 1H), 6.38 (dd, J = 15.6, 11.0 Hz, 1H), 6.04 (dd, J = 11.4, 11.0 Hz, 1H), 5.98 (dd, J = 11.0, 11.0 Hz, 1H), 5.66 (dd, J = 15.6, 6.0 Hz, 1H), 5.62 (dd, J = 15.6, 6.0 Hz, 1H), 5.48−5.32 (m, 6H), 4.87 (t, J = 5.0 Hz, 1H), 4.22 (td, J = 6.0, 6.0 Hz, 1H), 4.07 (dt, J = 6.4, 6.0 Hz, 1H), 4.02−3.91 (m, 2H), 3.90−3.80 (m, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.40 (m, 2H), 2.21 (td, J = 8.2, 6.9 Hz, 2H), 1.72 (m, 2H), 1.52 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.1, 128.6, 128.3, 128.2, 127.7, 127.0, 124.7, 124.5, 104.1, 74.5, 72.9, 64.8 (×2), 36.8, 33.7, 31.1, 26.0, 25.90 (×3), 25.86 (×3), 25.6, 21.9, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8; IR (neat) ν 2956, 2927, 2856, 1471, 1462, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4247.

Hexaene 23bb. According to the synthetic procedure of **23aa**, **23bb** (52.4 mg, 84.9 μmol) was synthesized from **25bb** (92.0 mg, 0.102 mmol) in 83% yield by using n-Bu_3SnH (0.40 mL, 1.50 mmol) and N-methylmorpholine oxide (119 mg, 1.02 mmol) in toluene (50 mL). Purification was performed twice by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{21}$ −10 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 15.6, 11.4 Hz, 1H), 6.38 (dd, J = 15.6, 11.0 Hz, 1H), 6.04 (dd, J = 11.4, 11.0 Hz, 1H), 5.98 (dd, J = 11.0, 11.0 Hz, 1H), 5.66 (dd, J = 15.6, 6.0 Hz, 1H), 5.62 (dd, J = 15.6, 6.0 Hz, 1H), 5.48−5.32 (m, 6H), 4.87 (t, J = 5.0 Hz, 1H), 4.22 (td, J = 6.0, 6.0 Hz, 1H), 4.07 (dt, J = 6.4, 6.0 Hz, 1H), 4.02−3.91 (m, 2H), 3.90−3.80 (m, 2H), 2.94 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.40 (m, 2H), 2.21 (td, J = 8.2, 6.9 Hz, 2H), 1.72 (m, 2H), 1.52 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.2, 128.6, 128.3, 128.2, 127.7, 126.9, 124.6, 124.5, 104.1, 74.4, 72.9, 64.9 (×2), 36.8, 33.7, 31.1, 26.0, 25.90 (×3), 25.87 (×3), 25.6, 21.9, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4240.

(14*S*,20*R*)-1aa. TMSOTf (0.15 mL, 0.83 mmol) was added to a solution of **23aa** (34.1 mg, 55.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (3.5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 45 min, and then H_2O (1.0 mL) was added. The resultant mixture was warmed to room temperature and stirred for 30 min. Then the mixture was extracted with EtOAc (8 mL × 2), and the combined organic layers were washed with aqueous 0.1 M HCl (4 mL), 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 (4 g, hexane to hexane/EtOAc 20/1) to afford the crude aldehyde **27aa**, which was used in the next reaction without further purification. Aldehyde **27aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.47 (dd, J = 15.1, 11.0 Hz, 1H), 6.38 (dd, J = 15.1, 11.0 Hz, 1H), 6.04 (dd, J = 11.0, 11.0 Hz, 1H), 5.91 (dd, J = 11.0, 11.0 Hz, 1H), 5.67 (dd, J = 15.1, 6.0 Hz, 1H), 5.62 (dd, J = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (q, J = 6.0 Hz, 2H), 4.07 (dt, J = 6.4, 6.0 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.84 (t, J = 5.9 Hz, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.40 (m, 4H), 1.50 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3

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Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 137.2, 136.7, 129.8, 129.3, 129.2, 128.3, 128.2, 128.0, 127.7, 126.9, 124.5, 124.3, 74.4, 72.9, 43.7, 36.8, 31.1, 26.1, 25.90 (×3), 25.87 (×3), 25.6, 20.1, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8.

A solution of $NaClO_2$ (80% purity, 55 mg, 0.49 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (80 mg, 0.52 mmol) in H_2O (1.5 mL) was added to a solution of the above crude aldehyde **27aa** in a mixture of *t*-BuOH (1.5 mL) and 2-methyl-2-butene (1.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Then the mixture was extracted with EtOAc (8 mL × 2), and the combined organic layers were washed with H_2O (4 mL) and brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) to afford the crude carboxylic acid **28aa**, which was used in the next reaction without further purification. Carboxylic acid **28aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (dt, *J* = 6.0, 6.0 Hz, 2H), 4.07 (dt, *J* = 6.4, 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.42−2.35 (m, 6H), 1.55−1.44 (m, 2H), 0.90 (s, 18H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.3, 128.3 (×2), 128.0, 127.6, 126.9, 124.6, 124.4, 74.4, 72.9, 36.8, 33.9, 31.1, 26.0, 25.91 (×3), 25.87 (×3), 25.6, 22.5, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M - H]^-$, found 587.3951.

TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol) was added to a solution of the above crude carboxylic acid **28aa** in THF (3.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, and then saturated aqueous NH_4Cl (4 mL) and 0.1 M HCl (10 mL) were successively added. The resultant mixture was extracted with EtOAc (10 and 5 mL), and 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 purified by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) to afford the crude (14*S*,20*R*)-**1aa**. Then the crude **1aa** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 40 min) to afford **1aa** (10.0 mg, 27.8 μmol) in 50% over three steps. (**14*S*,20*R*)-1aa**: pale yellow oil; $[\alpha]_D^{18}$ −28 (*c* 0.42, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.57 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.08 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.69 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.65 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50−5.32 (m, 6H), 4.18 (dt, *J* = 6.4, 6.4 Hz, 1H), 4.01 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.87 (m, 2H), 2.52−2.27 (m, 6H), 1.53 (m, 2H), 0.91 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.8, 137.2, 131.1, 130.8, 130.2, 129.7, 129.5, 129.3, 128.7, 128.1, 126.7, 126.5, 74.8, 73.1, 36.8, 31.2, 27.0, 26.6, 10.2, the C1, C2, and C3 peaks were missing due to broadening of the spectrum; IR (neat) ν 3348, 3010, 2956, 2923, 2851, 1726, 1451, 1389, 1274 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2222; UV (MeOH) λ_{max} 237 nm (ε 2.82 × 10^4).

(14*S*,20*S*)-1ab. According to the synthetic procedure of **1aa**, **1ab** (8.64 mg, 24.1 μmol) was synthesized from **23ab** (47.2 mg, 76.4 μmol) in 32% yield over three steps by using TMSOTf (0.21 mL, 1.2 mmol) and 2,6-lutidine (0.20 mL, 1.7 mmol) in CH_2Cl_2 (4.7 mL) for the first step, $NaClO_2$ (80% purity, 76 mg, 0.67 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (113 mg, 0.73 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (6.0 mL) for the second, and TBAF (1.0 M in THF, 0.76 mL, 0.76 mmol) in THF (5.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (8 g, hexane/EtOAc 4/1 to 3/1 to 3/2) for the second step and by flash column chromatography on silica gel (6 g, hexane/EtOAc/AcOH 40/60/0.05 to 30/70/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 36 min) for the third: pale yellow oil; $[\alpha]_D^{19}$ +13 (*c* 0.41, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 [M-H]$^-$, found 359.2223; UV (MeOH) λ_{max} 236 nm (ε 2.60 × 10^4). The other analytical data of **1ab** were identical with those of **1ba**.

(14*R*,20*R*)-1ba. According to the synthetic procedure of **1aa**, **1ba** (5.60 mg, 15.6 μmol) was synthesized from **23ba** (40.7 mg, 66.0 μmol) in 24% yield over three steps by using TMSOTf (0.18 mL, 0.99 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) in CH_2Cl_2 (4.2 mL) for the first step, $NaClO_2$ (80% purity, 68 mg, 0.60 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (99 mg, 0.64 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (4.5 mL) for the second, and TBAF (1.0 M in THF, 0.66 mL, 0.66 mmol) in THF (4.2 mL) for the third. Purification was performed by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) for the second step and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 33 min) for the third. Aldehyde **27ba**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.91 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (m, 2H), 4.07 (dt, *J* = 6.4, 6.0 Hz, 2H), 2.95 (t, *J* = 6.4 Hz. 2H), 2.84 (t, *J* = 5.9 Hz, 2H), 2.50 (t, *J* = 6.8 Hz, 2H), 2.40 (m, 4H), 1.50 (m, 2H), 0.90 (s, 18H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 137.2, 136.7, 129.8, 129.3, 129.2, 128.3, 128.2, 128.0, 127.4, 127.0, 124.6, 124.4, 74.5, 72.8, 43.7, 36.8, 31.1, 26.0, 25.91 (×3), 25.86 (×3), 25.6, 20.1, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8. Carboxylic acid **28ba**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (d, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (dt, *J* = 6.0, 6.0 Hz, 2H), 4.07 (dt, *J* = 6.4, 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.42−2.35 (m, 6H), 1.55−1.44 (m, 2H), 0.90 (s, 18H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.3, 128.3, 128.2, 128.0, 127.6, 127.0, 124.7, 124.4, 74.5, 72.9, 36.8, 33.9, 31.1, 26.0, 25.91 (×3), 25.87 (×3), 25.6, 22.5, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M - H]^-$, found 587.3974. (**14*R*,20*R*)-1ba**: pale yellow oil; $[\alpha]_D^{27}$ −16 (*c* 0.28, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.58 (dd, *J* = 15.6, 11.0 Hz, 1H), 6.51 (ddt, *J* = 15.1, 11.0. 1.4 Hz, 1H), 6.08 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.69 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.66 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.50−5.32 (m, 6H), 4.18 (dt, *J* = 6.4, 6.4 Hz, 1H), 4.01 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 5.5 Hz, 2H), 2.52−2.27 (m, 6H), 1.53 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.8, 137.1, 131.1, 130.8, 130.1, 129.6, 129.4, 129.3, 128.7, 128.1, 126.6, 126.5, 74.7, 73.1, 36.7, 31.2, 27.0, 26.5, 10.2, the C1, C2, and C3 peaks were missing due to broadening of the spectrum; IR (neat) ν 3380, 3011, 2958, 2925, 2855, 1713, 1556, 1415, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2243.

(14*R*,20*S*)-1bb. According to the synthetic procedure of **1aa**, **1bb** (4.59 mg, 12.8 μmol) was synthesized from **23bb** (22.0 mg, 35.6 μmol) in 36% yield over three steps by using TMSOTf (95 μL, 0.52 mmol) and 2,6-lutidine (95 μL, 0.82 mmol) in CH_2Cl_2 (2.2 mL) for the first step, $NaClO_2$ (80% purity, 35 mg, 0.31 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (54 mg, 0.35 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (3.0 mL) for the second, and TBAF (1.0 M in THF, 0.36 mL, 0.36 mmol) in THF (2.3 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 3/1) for the second step and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 42 min) for the third: pale yellow oil; $[\alpha]_D^{17}$ +22 (*c* 0.21, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2224. The other analytical data of **1bb** were identical with those of **1aa**.

Bioassay. Peritonitis was induced as described in ref 36. Synthetic **1aa**,**ab**,**ba**,**bb** (each 1 ng) were injected intravenously through the tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After

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2 h, peritoneal lavages were collected, PMN leucocyte numbers were counted, cell viability was determined using Trypan blue exclusion, and differential cell counts were monitored by Wright−Giemsa staining.

Statistical Analysis. Results are expressed as means ± SE. Differences between two groups were tested by the Student *t* test. Multiple comparisons were analyzed using ANOVA followed by the Tukey test. Significance levels of $P < 0.05$ and $P < 0.01$ were used.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra for all isolated compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01461.

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Notes

The authors declare no competing financial interest.

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(33) Generation of $(Bu_3P)(CO)_3CoH$ from $Co_2(CO)_6(PBu_3)_2$ and n-Bu_3SnH was proposed by Brown and co-worker. See: (a) Wegman, R. W.; Brown, T. L. *Organometallics* **1982**, *1*, 47. In addition, Isobe and co-workers proposed the generation of $(CO)_3CoH$ upon hydrosilylations of alkyne dicobalt hexacarbonyl complexes with trialkylsilane: (b) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485.

(34) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.

(35) The four isomers were separated by reverse-phase chiral HPLC (column CHIRALPAK AD-3R, 4.6 mm × 150 mm, eluent 50% CH_3CN/MeOH (4/1) in 0.1% aqueous AcOH for 5 min, 50−95% CH_3CN /MeOH (4/1) in 0.1% aqueous AcOH over 22.5 min, and then 95% CH_3CN /MeOH (4/1) in 0.1% aqueous AcOH for 8 min at 0.5 mL/min). Retention times of the synthetic **1**: t_R = 17.3 min for **1aa**, 14.6 min for **1ab**,**ba**, 14.0 min for **1bb**. Retention time of the natural **1aa**: t_R = 17.2 min.

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