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# Total Synthesis and Bioactivities of Two Proposed Structures of Maresin

**Kenji Sasaki, Daisuke Urabe, Hiroyuki Arai, Makoto Arita, and Masayuki Inoue*[a]**

*Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday*

**Abstract:** Maresin is a potent anti-inflammatory lipid mediator derived from docosahexaenoic acid (DHA). A highly convergent total synthesis of two proposed structures of C7-epimeric maresins from the four known fragments was achieved in 17 steps. The three key coupling reactions were the $BF_3$-mediated alkyne attack on the epoxide, chiral titanium complex-promoted enantioselective alkyne addition to the aldehyde, and a Julia–Kocienski olefination. The two synthesized diastereomers were found to be comparably active in blocking neutrophil infiltration in the acute peritonitis model.

**Keywords:** biological activity · fatty acids · inflammation · olefination · total synthesis

## Introduction

Endogenous lipid mediators play key roles in local controlling and programming of the acute innate inflammatory response and its resolution as an active biosynthetic process.[1] During resolution, specific fatty-acid-derived mediators, including resolvin E1[2] and protectin D1 (Figure 1), are generated within resolving exudates.[3] Serhan and co-workers demonstrated that these mediators are biosynthesized from omega-3 fatty acids, eicosapentanoic acid (EPA) or docosahexaenoic acid (DHA), and display potent multilevel anti-inflammatory and proresolving action.[4] More recently, maresin (**1**) was isolated from macrophages[5] as a novel lipid mediator generated from DHA, and was shown to exhibit activity equipotent to resolvin E1 and protectin D1. Accordingly, these anti-inflammatory molecules are expected to open new avenues in the development of treatment strategies for inflammatory diseases.

Maresin **1** is thought to be biosynthesized through a series of enzymatic reactions (Scheme 1): enantioselective hydroperoxydation of DHA at C14, epoxidation from (14*S*)-hydroperoxide **2**, and hydrolysis of **3**. Based on the postulated biosynthetic route and the MS/MS analyses of maresin and analogous molecules, **1** was proposed to have the (7,14*S*)-dihydroxy-(8*E*,10*E*,12*Z*)-conjugated triene substructure shown in Figure 1. The absolute stereochemistry of the C14-OH of the structure originates from **2**, although that of the C7-OH remains unestablished. Interestingly, the 1,8-dihydroxy groups and the conjugated triene are also found in the structures of both resolvin E1 and protectin D1, thereby suggesting the importance of these particular structural patterns for

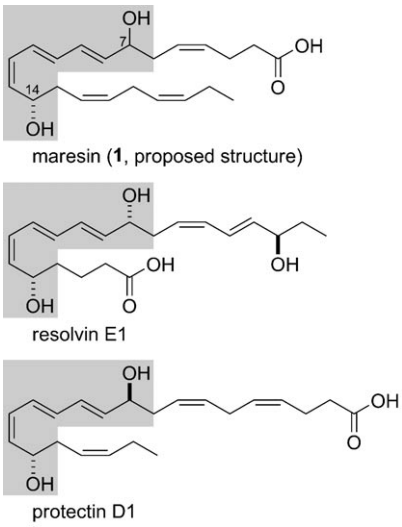


Figure 1. Structures of bioactive omega-3-polyunsaturated fatty acids. The 1,8-dihydroxy groups and conjugated trienes are highlighted in gray.

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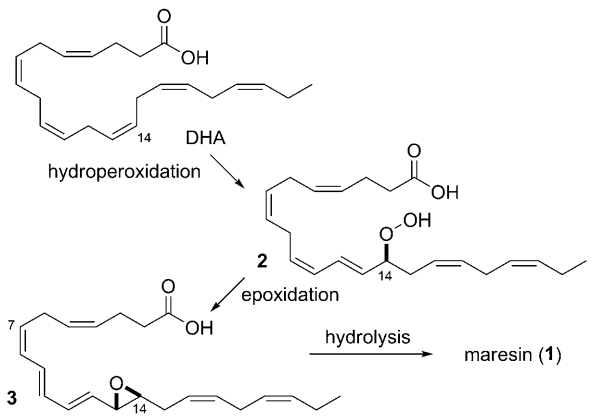


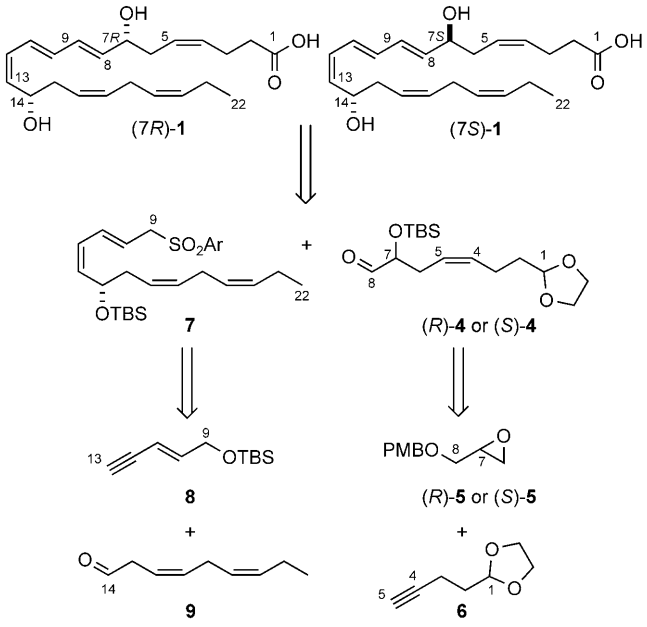

Scheme 1. Proposed biosynthesis of maresin (see Ref. [5]).

bioactivity. Herein, we report the total synthesis of the two proposed structures of C7-epimeric maresins (7*R*)-**1** and (7*S*)-**1**,[6,7] and their anti-inflammatory activities have been evaluated.

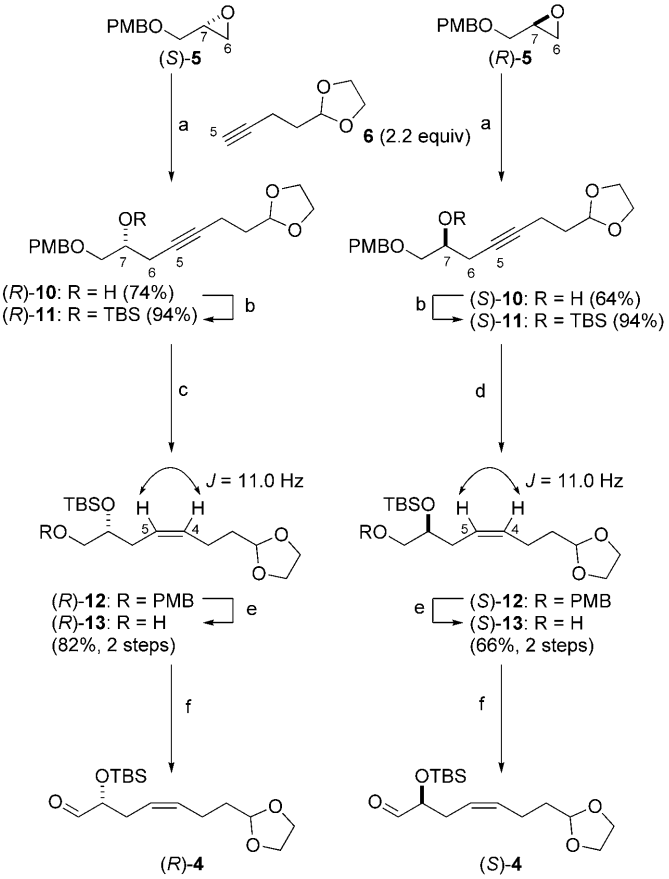
## Results and Discussion

Four readily available fragments (**5**, **6**, **8**, and **9**, Scheme 2) were designed to be employed for the convergent total syntheses of the highly unsaturated molecules (7*R*)-**1** and (7*S*)-**1**. The chemically unstable (*E*,*E*,*Z*)-triene unit of **1** was to be introduced at the last stage of the synthesis, and therefore **1** was retrosynthetically disconnected at the C8–9 bond. In the synthetic direction, the Julia–Kocienski olefination[8] of **7** with (*R*)-**4** and (*S*)-**4** would lead to (7*R*)-**1** and (7*S*)-**1**, respectively, in a stereoselective fashion. Both (*R*)-**4** and (*S*)-**4** were to be readily derived from the (*S*)- and (*R*)-glycidol derivatives **5**,[9] respectively, through alkynylation with **6**,[10] followed by *cis*-hydrogenation of the C4-triple bond. On the other hand, the C9–22 fragment **7** was planned to be prepared from enantioselective alkynylation of β,γ-unsaturated aldehyde **9**[11] with enyne **8**[12] and subsequent partial reduction of the triple bond. This concise and flexible synthetic route should provide access not only to (7*R*)-**1** and (7*S*)-**1**, but also to a variety of hydroxy and olefinic stereoisomers for future biological and SAR studies.

C1–8 fragments (*R*)-**4** and (*S*)-**4** were synthesized from the *para*-methoxybenzyl (PMB)-protected (*S*)- and (*R*)-glycidol **5**, respectively (Scheme 3). Lithium acetylide, generated from **6**, attacked the epoxide group of (*S*)-**5** and (*R*)-**5** by the action of $BF_3{\cdot}OEt_2$,[13] and led to the formation of homopropargyl alcohols (*R*)-**10** and (*S*)-**10**, respectively. The secondary hydroxy group of **10** was then protected as its TBS ether to afford **11**. Carefully controlled partial hydrogenation of the triple bond of **11** was realized by using either Lindlar's catalyst[14] or $Pd/BaSO_4$ in EtOAc, and subsequent oxidative removal of the PMB group of **12** with DDQ pro-




Scheme 2. Synthetic plan of the two proposed structures of maresin.



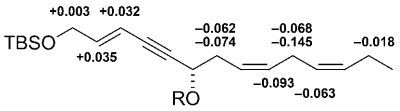

Scheme 3. Syntheses of the two C1–8 fragments. Reagents and conditions: a) *n*BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C→RT, **6** (2.2 equiv). b) TBSCl, imidazole, DMF, RT. c) $H_2$, Lindlar's cat., EtOAc, RT. d) $H_2$, $Pd/BaSO_4$, EtOAc, RT. e) DDQ, $CH_2Cl_2$, 0 °C. f) $(COCl)_2$, DMSO, $Et_3N$, $CHCl_2$, −78 °C→RT. THF = tetrahydrofuran; TBSCl = *tert*-butyldimethylsilyl chloride; DMF = *N*,*N*-dimethylformamide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMSO = dimethylsulfoxide.

vided **13**. Stereochemistries of the *cis*-olefins of the obtained (*R*)-**13** and (*S*)-**13** were confirmed from their coupling constants ($J_{4-5}$ = 11.0 Hz). Then, Swern oxidation of the primary alcohols (*R*)-**13** and (*S*)-**13** smoothly provided aldehydes (*R*)-**4** and (*S*)-**4**, respectively.[15]

Synthesis of the C9–22 fragment **7** is illustrated in Scheme 4. The known aldehyde **9** was routinely prepared from diyne **14**[16] in two steps. The two triple bonds of **14** were reduced to the two *cis*-double bonds in **15** ($J_{16-17}$ = 10.5 Hz and $J_{19-20}$ = 11.0 Hz), and the primary alcohol of **15** was oxidized to aldehyde **9**[10] by using *o*-iodoxybenzoic acid (IBX).[17] The enantioselective coupling reaction between **8** and **9** was challenging, this was mainly due to the chemical instability of β,γ-unsaturated aldehyde **9** towards both basic and acidic conditions. Lewis acid-mediated asymmetric alkynylation[18] of **9** typically resulted in decomposition of **9**. After many unsuccessful attempts, we found that the Ti(O*i*Pr)$_4$/(*R*)-BINOL reagent system effectively induced the enantioselective reaction.[19] Enyne **8** was treated with $Et_2Zn$ to prepare the corresponding alkynyl zinc compound, which was then added to aldehyde **9** in the presence of Ti(O*i*Pr)$_4$ and (*R*)-BINOL; this gave rise to propargyl alcohol **16** in an enantioselective fashion (69% *ee*). Despite the modest enantioselectivity, introduction of the C14-stereochemistry through this coupling chemistry greatly simplified the overall synthetic strategy.

To increase the enantiomeric excess, the secondary alcohol **16** (69% *ee*) was subjected to an enzymatic kinetic resolution by using lipase AK in vinylacetate, and this delivered enantiomerically pure alcohol **16** (97% *ee*) in 52% yield, along with the acetate in 30% yield.[20,21] The absolute stereochemistry of C14 was determined by the modified Mosher method, after **16** was derivatized to the corresponding (*S*)-MTPA **17a** and (*R*)-MTPA **17b** esters (Figure 2).[22] The differences in the $^1$H-chemical shifts ($\Delta\delta$) between **17a** and **17b** were calculated in order to determine the (*S*)-stereochemistry of the C14-alcohol. This structural assignment unambiguously demonstrated that the (*R*)-BINOL-based catalyst installed the desired (14*S*)-stereocenter in the reaction from **8** to **16**.

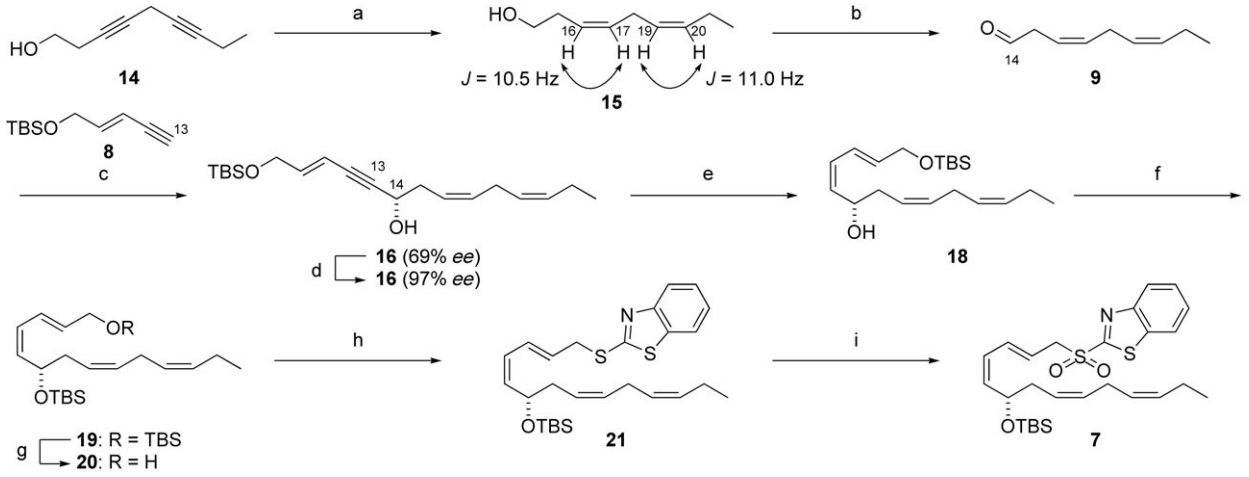



**17a**: R = (*S*)-MTPA
**17b**: R = (*R*)-MTPA

Figure 2. Determination of the absolute stereochemistry at C14. The numbers in bold are the difference ($\Delta\delta$) in the $^1$H chemical shifts between **17a** and **17b** ($\Delta\delta = \delta$ (**17a**)-$\delta$ (**17b**)) in $CD_3OD$. MTPA = 2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl.

Chemoselective hydrogenation of the triple bond of **16** (97% *ee*) into the double bond without reducing the other three olefins was achieved by treating **16** with copper/silver-activated zinc in methanol and water,[23] thereby affording tetraene **18** (Scheme 4). Silylation of the resultant secondary alcohol **18** using TBSOTf and $Et_3N$ was followed by the site-selective TBAF-promoted deprotection of bis-TBS ether **19**, which then led to **20**. To prepare for the Julia–Kocienski olefination,[8] sulfone **7** was synthesized from **20** in two steps: the primary hydroxy group of **20** was displaced by 2-mercaptobenzothiazole[24] under Mitsunobu conditions[25] to generate sulfide **21**, and the selective S-oxidation of **21** in the presence of the four potentially reactive olefins was accomplished by using ammonium molybdate[26] to deliver the C9–22 fragment **7**.

The most problematic reaction in our synthesis was the Julia–Kocienski coupling of the two highly unsaturated fragments, **4** and **7** (Scheme 5). The C9-conjugated anion, gener-




Scheme 4. Synthesis of the C9–22 fragment. Reaction conditions: a) $H_2$, Pd/$BaSO_4$, pyridine, DMF, RT, 80% yield. b) IBX, THF/DMSO, RT. c) **8** (4 equiv), $Et_2Zn$ (4 equiv), Ti(O*i*Pr)$_4$ (1 equiv), (*R*)-BINOL (0.4 equiv), $Et_2O$, RT; 63% yield over 2 steps. d) Lipase AK, vinylacetate, 55 °C, 52% yield. e) Zn, MeOH/$H_2O$ (1:1), RT, 94% yield. f) TBSOTf, $Et_3N$, $CH_2Cl_2$, −78 °C → RT, 91% yield. g) TBAF, THF, −10 °C, 92% yield. h) 2-mercaptobenzothiazole, DIAD, $PPh_3$, THF, RT, 93% yield. i) $H_2O_2$, EtOH, RT, 72% yield. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; TBAF = tetra-*n*-butylammonium fluoride; DIAD = azodicarboxylic diisopropylate.

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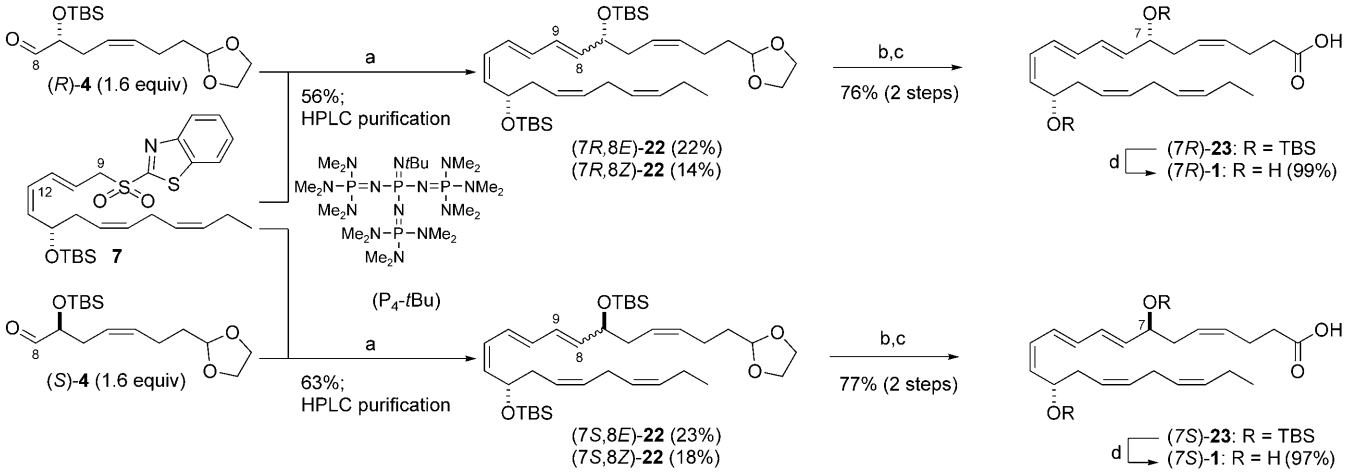


Scheme 5. Total syntheses of the two proposed structures of maresin. Reaction conditions: a) $P_4$-*t*Bu, $CH_3CN$, −40 °C. b) TMSOTf, lutidine, $CH_2Cl_2$, −20 °C, $H_2O$, RT. c) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH/$H_2O$ (1:1), RT. d) TBAF, THF, RT.

ated by deprotonation of **7** with typical bases (e.g., *n*BuLi, $KN(TMS)_2$), underwent facile C12-olefin isomerization prior to slow nucleophilic attack on aldehyde **4**; this resulted in the formation of adduct **22** in low yield as a mixture of stereoisomers at C8 and C12. Changing the sulfone moiety of **7** to the 1-phenyl-1*H*-tetrazol-5-yl, 1-*tert*-butyl-1*H*-tetrazol-5-yl or 3,5-bis(trifluoromethyl)phenyl sulfones did not improve the yield or stereoselectivity. After extensive optimization, the highly reactive "naked" anion, generated from **7** by using phosphazene base $P_4$-*t*Bu in MeCN,[27] underwent facile addition to (*R*)-**4** or (*S*)-**4**, thereby resulting in **22** as a mixture of C8-stereoisomers (8*E*/8*Z* = 3:2) in approximately 60 % yield. HPLC purification of the obtained coupling adducts from (*R*)-**4** and (*S*)-**4** yielded pure (7*R*,8*E*)-**22** (22 % based on **7**) and (7*S*,8*E*)-**22** (23 % based on **7**), respectively.

Finally, the chemically sensitive hexaenes (7*R*,8*E*)-**22** and (7*S*,8*E*)-**22** were converted to the proposed structures of maresin through three steps. Kita's conditions effectively[6b,28] removed the cyclic acetal moiety of **22** in the presence of the acid-labile allylic TBS ethers and the triene, thus giving rise to the aldehyde; $NaClO_2$-mediated oxidation of which gave carboxylic acid **23**. Desilylation of (7*R*)-**23** and (7*S*)-**23** with TBAF delivered the targeted (7*R*)-**1** and (7*S*)-**1**, respectively. Intriguingly, the $^1H$ and $^{13}C$ NMR spectra of (7*R*)-**1** and (7*S*)-**1** in $CD_3OD$ were identical, while their retention times on an ODS HPLC were different ($t_R$(7*R*-**1**) = 12.4 min, $t_R$(7*S*-**1**) = 11.6 min).[29] The stereochemistry of the unstable (8*E*,10*E*,12*Z*)-conjugated triene units of both (7*R*)-**1** and (7*S*)-**1** was confirmed by the $^1H$–$^1H$ coupling constants shown in Figure 3.

Next, we evaluated the biological activity of synthetic (7*R*)-**1** and (7*S*)-**1** by using an in vivo inflammation model (Figure 4). Zymosan A, a glucan from the yeast cell wall, was used to induce acute peritonitis in mice. Intravenous administration of (7*R*)-**1** and (7*S*)-**1** as low as 1.0 and 10 ng significantly blocked neutrophil infiltration after 2 h in the inflamed peritoneal cavity in a comparable manner.[5]

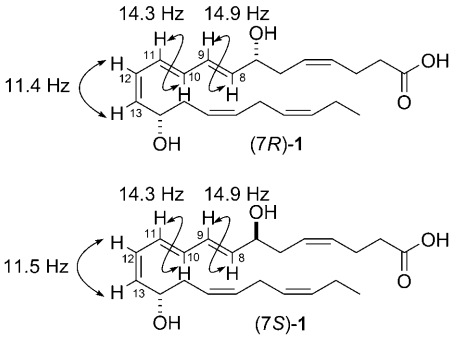


Figure 3. $^1H$-$^1H$ coupling constants of the conjugated triene unit of (7*R*)-**1** and (7*S*)-**1**.

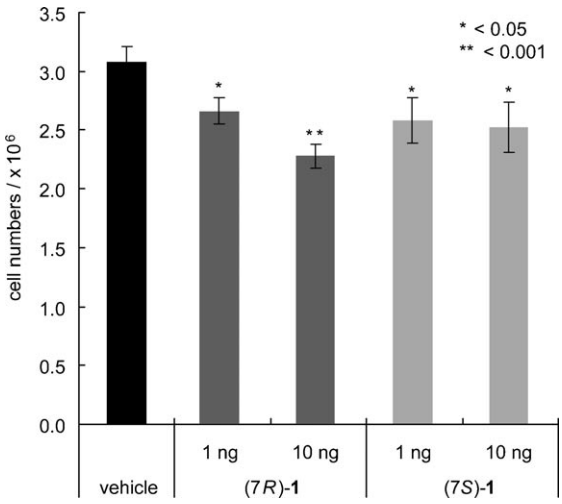


Figure 4. Synthetic (7*R*)-**1** and (7*S*)-**1** reduced neutrophil infiltration in zymosan-induced peritonitis. Maresin or vehicle alone was injected into the mouse followed by zymosan A injection. At 2 h, peritoneal lavages were collected and cells were enumerated.

  

## Conclusions

The convergent total synthesis of two proposed structures of maresin ((7*R*)-**1** and (7*S*)-**1**) was achieved in 17 steps from the four fragments **5**, **6**, **8**, and **9**. $BF_3$-mediated alkyne attack on the epoxide, chiral titanium complex-promoted enantioselective alkyne addition to the aldehyde, and Julia–Kocienski olefination were the three key coupling reactions. Intriguingly, both synthetic (7*R*)-**1** and (7*S*)-**1** were found to exhibit comparable anti-inflammatory properties in blocking neutrophil infiltration. As the highly convergent and flexible strategy developed here would enable the synthesis of a variety of hydroxy and olefinic stereoisomers, further studies will focus on the preparation of other isomers of maresin and detailed biological analysis of these synthesized compounds.

## Experimental Section

All reactions sensitive to air or moisture were carried out under an atmosphere of argon or in dry or freshly distilled solvents under anhydrous conditions, unless otherwise noted. All other reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.) and flash column chromatography was performed using 50–60 μm Silica Gel 60 (Kanto Chemical Co., Inc.). $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-ECX-500, JNM-ECA-500, or a JNM-ECS-400 spectrometer. Chemical shifts were reported in ppm on the $\delta$ scale relative to residual $CHCl_3$ ($\delta=7.26$ for $^1$H NMR and $\delta=77.0$ for $^{13}$C NMR), $C_6HD_5$ ($\delta=7.16$ for $^1$H NMR), and $CD_2HOD$ ($\delta=3.30$ for $^1$H NMR and $\delta=49.0$ for $^{13}$C NMR) as an internal reference. Signal patterns are indicated as s = singlet; d = doublet; m = multiple. Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer, or a JASCO FT/IR-4100 spectrometer. High-resolution mass spectra were measured on a JEOL JMS-700 or a Bruker microTOFII. Optical rotations were recorded on a JASCO DIP-370 Polarimeter or a JASCO DIP-1000 Digital Polarimeter.

**Alcohol (*R*)-10:** *n*BuLi (1.6 M in hexane, 2.6 mL, 4.1 mmol) was added to a solution of **6** (770 mg, 4.53 mmol, a 1.77:1 mixture of **6** and benzene) in THF (4.5 mL) at −78 °C. After the solution was stirred for 5 min, $BF_3{\cdot}OEt_2$ (0.51 mL, 4.1 mmol) was added to the mixture. Then, a solution of **5** (0.40 g, 2.1 mmol) in THF (2.4 mL) was added to the mixture at −78 °C, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the resulting solution was extracted twice with $Et_2O$. Combined organic layers were washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. Flash chromatography on silica gel (hexane/EtOAc 10:1 to 4:1) afforded (*R*)-**10** (491 mg, 1.53 mmol) in 74% yield: pale yellow viscous oil; $[\alpha]_D^{19}=-5.1$ ($c=0.6$, $CHCl_3$); IR (neat): $\tilde{\nu}=$ 3445, 2883, 1611, 1513, 1247, 1034 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta=$ 1.83 (2H, td, $J=7.5$, 4.6 Hz, $CH_2$-C$H_2$-CH), 2.28 (2H, tt, $J=7.5$, 2.9 Hz, C$H_2$-$CH_2$-CH), 2.38 (2H, dt, $J=5.7$, 2.9 Hz, HOCHC$H_2$-), 2.50 (1H, brs, O$H$), 3.44 (1H, dd, $J=9.8$, 6.9 Hz, C$H_A$H$_B$-OPMB), 3.54 (1H, dd, $J=9.8$, 4.0 Hz, CH$_A$H$_B$-OPMB), 3.79 (3H, s, OC$H_3$), 3.82–3.96 (5H, m, O-C$H_2$C$H_2$-O, C$H$-OH), 4.48 (2H, s, C$H_2$-$C_6H_5$-OCH$_3$), 4.93 (1H, t, $J=$ 4.6 Hz, O-C$H$-O), 6.87 (2H, d, $J=9.2$ Hz, aromatic $H$), 7.25 ppm (2H, d, $J=9.2$ Hz, aromatic $H$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=$13.6, 23.9, 33.0, 55.2, 64.9, 69.0, 72.6, 73.0, 81.7, 103.4, 113.7, 129.3, 130.0, 159.2 ppm; HRMS (FAB) calcd for $C_{18}H_{24}O_5Cs$ 453.0678 $[M+Cs]^+$, found 453.0683.

**TBS ether (*R*)-11:** *tert*-Butyldimethylsilyl chloride (494 mg, 3.28 mmol) was added to a mixture of (*R*)-**10** (350 mg, 1.09 mmol) and imidazole (446 mg, 6.55 mmol) in DMF (5.5 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then poured into ice-cold water. The resulting mixture was extracted twice with EtOAc. Combined organic layers were washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 10:0 to 20:1) to afford (*R*)-**11** (447 mg, 1.03 mmol) in 94% yield: colorless oil; $[\alpha]_D^{20}=-0.6$ ($c=0.48$, $CHCl_3$); IR (neat): $\tilde{\nu}=2931$, 2857, 1513, 1248, 1123, 1038 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta=0.06$ (3H, s, C$H_3$ of TBS), 0.08 (3H, s, C$H_3$ of TBS), 0.88 (9H, s, *t*Bu of TBS), 1.82 (2H, td, $J=7.5$, 4.6 Hz, $CH_2$-C$H_2$-CH), 2.25–2.32 (3H, m, C$H_A$H$_B$-CC, C$H_2$-CC), 2.37–2.44 (1H, m, CH$_A$H$_B$-CC), 3.41 (1H, dd, $J=10.3$, 5.7 Hz, C$H_A$H$_B$-OPMB), 3.47 (1H, dd, $J=10.3$, 4.6 Hz, CH$_A$H$_B$-OPMB), 3.80 (3H, s, OC$H_3$), 3.83–3.96 (5H, m, O-C$H_2$C$H_2$-O, C$H$-OTBS), 4.46 (2H, s, C$H_2$-$C_6H_5$-OCH$_3$), 4.95 (1H, t, $J=4.6$ Hz, O-C$H$-O), 6.87 (2H, d, $J=9.2$ Hz, aromatic $H$), 7.25 ppm (2H, d, $J=9.2$ Hz, aromatic $H$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-4.7$, −4.6, 13.7, 18.1, 25.0, 25.8, 33.2, 55.2, 64.9, 70.8, 73.0, 73.5, 80.5, 103.3, 113.7, 129.1, 130.5, 159.1 ppm; HRMS (FAB) calcd for $C_{24}H_{38}O_5SiCs$ 567.1543 $[M+Cs]^+$, found 567.1553.

***cis*-olefin (*R*)-12:** Lindlar catalyst (176 mg) was added to a mixture of (*R*)-**11** (352 mg, 0.81 mmol) and quinoline (20 μL) in EtOAc (32 mL). The mixture was vigorously stirred at room temperature for 1 h under an atmospher of $H_2$ (1 atom, balloon). The reaction mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated in vacuo to give the crude (*R*)-**12** (352 mg, 0.805 mmol), which was used for the next reaction without further purification. A portion of crude (*R*)-**12** was purified by flash column chromatography to give the pure (*R*)-**12**: $[\alpha]_D^{17}=-0.1$ ($c=0.25$, $CHCl_3$); IR (neat): $\tilde{\nu}=2952$, 2928, 2856, 1613, 1514, 1249, 1132, 1037 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta=0.04$ (3H, s, C$H_3$ of TBS), 0.05 (3H, s, C$H_3$ of TBS), 0.87 (9H, s, *t*Bu of TBS), 1.70 (2H, td, $J=7.4$, 4.6 Hz, $CH_2$-C$H_2$-CH), 2.12–2.34 (4H, m, C$H_2$-C=C-C$H_2$), 3.35 (2H, d, $J=5.8$ Hz, C$H_2$-OPMB), 3.81 (3H, s, OC$H_3$), 3.82–3.98 (5H, m, O-C$H_2$C$H_2$-O, C$H$-OTBS), 4.44 (2H, s, C$H_2$-$C_6H_5$-OCH$_3$), 4.85 (1H, t, $J=4.6$ Hz, O-C$H$-O), 5.43 (1H, dd, $J=10.9$, 5.8 Hz, C$H_A$=CH$_B$), 5.47 (1H, dd, $J=10.9$, 6.3 Hz, CH$_A$=C$H_B$), 6.86 (2H, d, $J=8.6$ Hz, aromatic $H$), 7.25 ppm (2H, d, $J=9.2$ Hz, aromatic $H$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-4.7$, −4.5, 18.1, 22.0, 25.0, 25.8, 32.5, 33.7, 55.2, 64.8, 71.5, 72.9, 74.1, 104.1, 113.6, 126.2, 129.1, 130.5, 159.0 ppm; HRMS (FAB) calcd for $C_{24}H_{40}O_5SiCs$ 569.1699 $[M+Cs]^+$, found 569.1700.

**Alcohol (*R*)-13:** DDQ (187 mg, 0.82 mmol) was added to a mixture of (*R*)-**12** (240 mg, 0.55 mmol) in $CH_2Cl_2$ (5.5 mL) and phosphate buffer (pH 7, 0.55 mL) at 0 °C. After being stirred for 1 h at 0 °C, $MgSO_4$ (200 mg) was added to the reaction mixture, and the resulting mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and purified by flash chromatography on silica gel (hexane/EtOAc 10:0 to 8:1) to afford (*R*)-**13** (143 mg, 0.451 mmol) in 82% yield: colorless oil; $[\alpha]_D^{23}=-22$ ($c=0.42$, $CHCl_3$); IR (neat): $\tilde{\nu}=3447$, 2953, 2857, 1472, 1254, 1102, 1040 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.088$ (3H, s, C$H_3$ of TBS), 0.091 (3H, s, C$H_3$ of TBS), 0.90 (9H, s, *t*Bu of TBS), 1.71 (2H, td, $J=7.5$, 5.2 Hz, $CH_2$-C$H_2$-CH), 1.89 (1H, brs, O$H$), 2.18 (2H, br dt, $J=7.4$, 7.4 Hz, C=C-C$H_2$-$CH_2$-), 2.28 (2H, dd, $J=7.4$, 7.4 Hz, TBSOCH-C$H_2$), 3.43 (1H, dd, $J=11.5$, 5.2 Hz, C$H_A$H$_B$-OH), 3.53 (1H, dd, $J=11.5$, 4.0 Hz, CH$_A$H$_B$-OH), 3.73–3.79 (1H, m, C$H$-OTBS), 3.82–3.98 (4H, m, OC$H_2$C$H_2$O), 4.86 (1H, t, $J=5.2$ Hz, O-C$H$-O), 5.39 (1H, dt, $J=11.0$, 7.5 Hz, TBSOCHC$H$=CH), 5.48 ppm (1H, dt, $J=11.0$, 7.4 Hz, TBSOCHCH=C$H$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$, −4.5, 18.1, 22.0, 25.8, 31.8, 33.6, 64.9, 65.8, 72.6, 104.0, 125.4, 131.1 ppm; HRMS (FAB) calcd for $C_{16}H_{32}O_4SiCs$ 449.1124 $[M+Cs]^+$, found 449.1126.

**Aldehyde (*R*)-14:** Dimethyl sulfoxide (40 μL, 570 μmol) in $CH_2Cl_2$ (0.6 mL) was added to a solution of $(COCl)_2$ (24 μL, 280 μmol) in $CH_2Cl_2$ (0.6 mL) at −78 °C. After 15 min at −78 °C, a solution of (*R*)-**13** (30 mg, 95 μmol) in $CH_2Cl_2$ (0.7 mL) was added to the solution. After the reaction mixture was stirred for 10 min at −78 °C, $Et_3N$ (132 μL, 948 μmol) was added, and the solution was allowed to warm to 10 °C over 40 min. The reaction was then quenched with saturated aqueous $NH_4Cl$. The resulting mixture was extracted twice with EtOAc, the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated to give (*R*)-**14** (35 mg) as a pale yellow oil, which was used for the next reaction without further purification.

  

**Alcohol (*S*)-10:** Following the same procedure for synthesis of (*R*)-**10**, (*S*)-**10** (1.06 g, 3.31 mmol) was synthesized in 64% yield by treating **6** (1.93 g, 11.3 mmol, as a 1.77:1 mixture of **6** and benzene) with (*R*)-**5** (1.00 g, 5.15 mmol); $[\alpha]_D^{24} = +5.1$ ($c = 1.1$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3466$, 2887, 1612, 1514, 1249, 1132, 1036 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta =$ 1.83 (2H, td, $J = 7.5$, 4.6 Hz, $CH_2$-C$H_2$-CH), 2.28 (2H, brt, $J = 7.5$ Hz, C$H_2$-$CH_2$-CH), 2.38 (2H, br d, $J = 5.7$ Hz, HOCHC$H_2$-), 2.61 (1H, d, $J =$ 4.1 Hz, O*H*), 3.44 (1H, dd, $J = 9.7$, 6.9 Hz, C$H_A$H$_B$-OPMB), 3.54 (1H, dd, $J = 9.7$, 4.0 Hz, CH$_A$$H_B$-OPMB), 3.79 (3H, s, OC$H_3$), 3.82–3.96 (5H, m, O-C$H_2$C$H_2$-O, C*H*-OH), 4.48 (2H, s, C$H_2$-$C_6H_5$-OCH$_3$), 4.93 (1H, t, $J =$ 4.6 Hz, O-C*H*-O), 6.87 (2H, d, $J = 8.6$ Hz, aromatic *H*), 7.25 ppm (2H, d, $J = 8.6$ Hz, aromatic *H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 13.7$, 23.9, 33.0, 55.2, 64.9, 69.0, 72.6, 73.0, 81.7, 103.4, 113.8, 129.4, 130.0, 159.2 ppm; HRMS (FAB) calcd for $C_{18}H_{24}O_5Cs$ 453.0678 $[M+Cs]^+$, found 453.0685.

**TBS ether (*S*)-11:** Following the same procedure for synthesis of (*R*)-**11**, (*S*)-**11** (900 mg, 2.07 mmol) was synthesized from (*S*)-**10** (700 mg, 2.19 mmol) in 94% yield; $[\alpha]_D^{17} = +1.1$ ($c = 0.58$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 2929, 2855, 1514, 1249, 1124, 1038 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta =$ 0.06 (3H, s, C$H_3$ of TBS), 0.08 (3H, s, C$H_3$ of TBS), 0.88 (9H, s, *t*Bu of TBS), 1.82 (2H, td, $J = 7.5$, 4.6 Hz, $CH_2$-C$H_2$-CH), 2.24–2.31 (3H, m, C$H_A$H$_B$-CC, C$H_2$-CC), 2.37–2.43 (1H, m, CH$_A$$H_B$-CC), 3.41 (1H, dd, $J =$ 10.3, 5.7 Hz, C$H_A$H$_B$-OPMB), 3.47 (1H, dd, $J = 10.3$, 4.6 Hz, CH$_A$$H_B$-OPMB), 3.80 (3H, s, OC$H_3$), 3.83–3.97 (5H, m, O-C$H_2$C$H_2$-O, C*H*-OTBS), 4.47 (2H, s, C$H_2$-$C_6H_5$-OCH$_3$), 4.95 (1H, t, $J = 4.6$ Hz, O-C*H*-O), 6.87 (2H, d, $J = 8.6$ Hz, aromatic *H*), 7.25 ppm (2H, d, $J = 8.6$ Hz, aromatic *H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = -4.6$, 13.7, 18.2, 25.0, 25.8, 33.2, 55.2, 64.9, 70.8, 73.0, 73.5, 80.5, 103.3, 113.7, 129.2, 130.5, 159.0 ppm; HRMS (FAB) calcd for $C_{24}H_{38}O_5SiCs$ 567.1543 $[M+Cs]^+$, found 567.1533.

**Alcohol (*S*)-13:** Pd/$BaSO_4$ (5%, 50 mg) was added to a solution of (*S*)-**11** (100 mg, 0.230 mmol) and pyridine (18 μL, 0.23 mmol) in EtOAc (9.2 mL). The mixture was vigorously stirred for 1 h under an atmosphere of $H_2$ (1 atm, balloon) at room temperature. The residue was filtered through a pad of Celite with EtOAc. The filtrate was concentrated in vacuo to give crude (*S*)-**12**, which was then used for the next reaction without further purification. DDQ (58 mg, 0.26 mmol) was added to a solution of the crude (*S*)-**12** in $CH_2Cl_2$ (1.7 mL) and phosphate buffer (pH 7, 70 μL) at 0°C. The reaction mixture was stirred for 1 h and allowed to warm to room temperature. $MgSO_4$ (200 mg) was added to the reaction mixture, and the resulting mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and purified by flash chromatography on silica gel (hexane/EtOAc 1:0 to 50:1 to 10: 1 to 5:1) to afford (*S*)-**13** (48 mg, 0.15 mmol) in 66% yield over 2 steps: colorless oil; $[\alpha]_D^{28} = +22$ ($c = 0.47$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3481$, 2953, 2929, 2857, 1472, 1254, 1103, 1041 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 0.08$ (3H, s, C$H_3$ of TBS), 0.09 (3H, s, C$H_3$ of TBS), 0.89 (9H, s, *t*Bu of TBS), 1.71 (2H, dt, $J = 7.3$, 5.0 Hz, $CH_2$-C$H_2$-CH), 2.18 (2H, dt, $J = 7.8$, 7.3 Hz, C=C-C$H_2$-$CH_2$-), 2.28 (2H, dd, $J = 6.9$, 6.9 Hz, TBSOCH-C$H_2$), 3.43 (1H, dd, $J = 10.6$, 5.0 Hz, C$H_A$H$_B$-OH), 3.52 (1H, dd, $J = 10.6$, 3.2 Hz, CH$_A$$H_B$-OH), 3.73–3.79 (1H, m, C*H*-OTBS), 3.82–3.98 (4H, m, OC$H_2$C$H_2$O), 4.85 (1H, t, $J = 5.0$ Hz, O-C*H*-O), 5.39 (1H, dt, $J = 11.0$, 7.3 Hz, TBSOCHC*H*=CH), 5.48 ppm (1H, dt, $J = 11.0$, 7.8 Hz, TBSOCHCH=C*H*); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, $-4.5$, 18.1, 22.0, 25.8, 31.8, 33.6, 64.8, 65.8, 72.6, 104.0, 125.4, 131.1 ppm; HRMS (FAB) calcd for $C_{16}H_{32}O_4SiCs$ 449.1124 $[M+Cs]^+$, found 449.1118.

**Aldehyde (*S*)-4** was synthesized from (*S*)-**13** (15 mg, 47 μmol) by using the same procedure for synthesis of (*R*)-**4** and then used for the next reaction without further purification.

**Diene 15**: A mixture of **14** (3.5 g, 26 mmol), pyridine (10.4 mL, 128 mmol) and 5% Pd-$BaSO_4$ (1.75 g) in DMF (257 mL) was vigorously stirred for 1 h under an atmosphere of $H_2$ (1 atm, balloon) at room temperature. Then 5% Pd-$BaSO_4$ (1.75 g) was added to the reaction mixture, and the mixture was stirred for an additional 2 h. The suspension was filtered through a pad of Celite with EtOAc, and the filtrate was washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 5:1 to 2:1) to afford **14** (3.3 g, 21 mmol, as a 3.4:1 mixture of **14** and $Et_2O$) in 80% yield: $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (3H, t, $J = 7.3$ Hz, $CH_2$-C$H_3$), 2.07 (2H, dq, $J = 7.8$, 7.3 Hz, C$H_2$-$CH_3$), 2.35 (2H, dt, $J = 7.8$, 6.4 Hz, HOCH$_2$-C$H_2$-), 2.82 (2H, t, $J = 6.9$ Hz, CH=CH-C$H_2$-CH=CH), 3.65 (2H, t, $J = 6.4$ Hz, HOC$H_2$), 5.30 (1H, dtt, $J = 11.0$, 7.3, 1.4 Hz, CH=C*H*-$CH_2$-CH=CH), 5.35–5.43 (2H, m, C*H*=CH-$CH_2$-CH=C*H*), 5.54 ppm (1H, dtt, $J = 10.5$, 7.8, 0.9 Hz, CH=CH-$CH_2$-C*H*=CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 20.5, 25.6, 30.7, 62.2, 125.3, 126.8, 131.5, 132.2 ppm; HRMS (FAB) calcd for $C_9H_{17}O$ 141.1279 $[M+H]^+$, found 141.1279.

**Propargyl alcohol 16**: IBX (3.2 g, 11.4 mmol) was added to a solution of **15** (920 mg, 5.7 mmol, a 3.4:1 mixture of **15** and $Et_2O$) in THF (22.8 mL) and DMSO (5.7 mL) at 0°C. The suspension was stirred for 5 h at room temperature. The mixture was filtered through a pad of Celite with $Et_2O$, and the filtrate was washed with saturated aqueous $Na_2S_2O_3 \cdot 5H_2O$, saturated aqueous $NaHCO_3$, $H_2O$ and brine, and dried over anhydrous $Na_2SO_4$. The residue was filtered, concentrated in vacuo (80 mmHg, 37°C) to afford **9** (900 mg) as a pale yellow oil, which was used for the next reaction without purification. A mixture of $Et_2Zn$ (1.1 M toluene, 20.7 mL, 22.8 mmol) and **8** (4.48 g, 22.8 mmol) were refluxed for 3 h. After the solution was cooled to room temperature, (*R*)-BINOL (653 mg, 2.28 mmol), $Et_2O$ (25 mL) and Ti(O*i*Pr)$_4$ (1.7 mL, 5.7 mmol) were added sequentially. The reaction mixture was stirred for 1 h, and then a solution of crude **9** in $Et_2O$ (51 mL) was added to the mixture. After being stirred for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$. The resulting suspension was filtered through a pad of Celite with $Et_2O$. The filtrate was washed with brine and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 20:1) to afford **16** (1.2 g, 3.6 mmol) in 63% yield. The optical purity of **16** was determined as 69% *ee* from the integration of the $^1H$ NMR spectrum after derivatization into the corresponding MTPA ester.

**Kinetic resolution of propargyl alcohol 16:** A mixture of **16** (1.1 g, 3.3 mmol, 69% *ee*) and lipase AK (1.1 g) in vinylacetate (16.4 mL) was stirred at 55°C for 22 h. The suspension was filtered through a pad of Celite with hexane, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/AcOEt 100:0 to 30:1) to afford **16** (576 mg, 1.72 mmol) in 52% yield, and the corresponding acetate in 30% yield (368 mg, 0.98 mmol). The optical purity of **16** was determined as 97% *ee* from the integration of $^1H$ NMR after derivatization into the corresponding MTPA ester: $[\alpha]_D^{17} = -19$ ($c =$ 0.41, $CHCl_3$); IR (neat): $\tilde{\nu} = 3358$, 2957, 1463, 1376, 1256, 1130 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 0.06$ (6H, s, C$H_3$ of TBS), 0.90 (9H, s, *t*Bu of TBS), 0.96 (3H, t, $J = 7.5$ Hz, $CH_2$-C$H_3$), 1.99 (1H, brs, O*H*), 2.06 (2H, dq, $J = 7.5$, 7.4 Hz, C$H_2$-$CH_3$) 2.52 (2H, br dd, $J = 6.9$, 6.9 Hz, HOC-C$H_2$-), 2.83 (2H, dd, $J = 6.9$, 6.9 Hz, C=CH-C$H_2$-CH=C), 4.21–4.23 (2H, m, C$H_2$-OTBS), 4.52 (1H, t, $J = 6.3$ Hz, C*H*-OH), 5.27–5.32 (1H, m, C*H*=CH-Et), 5.36–5.42 (1H, m, CH=C*H*-Et), 5.47–5.52 (1H, m, $CH_2$-C*H*=CH-$CH_2$-CH=C), 5.56–5.62 (1H, m, $CH_2$-CH=C*H*-$CH_2$-CH=C), 5.77 (1H, dd, $J = 16.0$, 2.3 Hz, CH=C*H*-CC), 6.19 ppm (1H, dt, $J = 16.0$, 4.0 Hz, C*H*=CH-CC); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = -5.4$, 14.2, 18.3, 20.5, 25.7, 25.8, 35.7, 62.4, 62.8, 83.3, 89.8, 108.0, 123.7, 126.7, 132.2, 132.3, 142.8 ppm; HRMS (FAB) calcd for $C_{20}H_{34}O_2SiCs$ 467.1382 $[M+Cs]^+$, found 467.1385.

**(*S*)-MTPA derivatives 17a:** A mixture of propargyl alcohol **16** (1.6 mg, 4.8 μmol), (*R*)-MTPACl (2 μL, 10 μmol), and $Et_3N$ (3 μL, 20 μmol) in $CH_2Cl_2$ (0.1 mL) was stirred for 1 h at room temperature. Then a catalytic amount of DMAP was added. After being stirred for 1 h, the reaction mixture was directly subjected to flash chromatography on silica gel (hexane/EtOAc 5:1) to afford (*S*)-MTPA derivatives **17a** (2.6 mg, 4.7 μmol) in 98% yield: colorless oil; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta =$ 0.082 (6H, s, C$H_3$ of TBS), 0.920 (9H, s, *t*Bu of TBS), 0.945 (3H, t, $J =$ 7.8 Hz, $CH_2$-C$H_3$), 2.030 (2H, dq, $J = 7.8$ Hz, C$H_2$-$CH_3$), 2.541 (1H, dd, $J = 14.2$, 6.4 Hz, C$H_A$H$_B$-CHOMTPA), 2.604 (1H, dd, $J = 13.7$, 6.8 Hz, CH$_A$$H_B$-CHOMTPA), 2.650 (1H, ddd, $J = 15.1$, 7.3, 7.3 Hz, C=CH-C$H_A$H$_B$-CH=C), 2.727 (1H, ddd, $J = 15.6$, 7.3, 7.3 Hz, C=CH-CH$_A$$H_B$-CH=C), 3.566 (3H, s, OMe), 4.253 (2H, dd, $J = 4.1$, 2.3 Hz, C$H_2$-OTBS), 5.204 (1H, dtt, $J = 11$, 7.3, 1.4 Hz, C*H*=CH-$CH_2CH_3$), 5.309 (1H, ddt, $J =$ 11, 7.3, 1.4 Hz, MTPAOCHCH$_2$-C*H*=CH), 5.354 (1H, ddt, $J = 11$, 7.3, 1.4 Hz, CH=C*H*-$CH_2CH_3$), 5.456 (1H, dtt, $J = 11$, 7.3, 1.4 Hz,

  

MTPAOCHCH$_2$-CH=C*H*), 5.682 (1H, td, $J$=6.4, 1.4 Hz, C*H*-OMTPA), 5.781 (1H, ddt, $J$=16, 1.8, 1.8 Hz, TBSOCH$_2$-CH=C*H*), 6.257 (1H, ddd, $J$=16, 4.1 Hz, TBSOCH$_2$-C*H*=CH), 7.37–7.44 (3H, m, aromatic *H*), 7.50–7.54 ppm (2H, m, aromatic *H*).

**(*R*)-MTPA derivatives 17b:** Following the same procedure for synthesis of (*S*)-MTPA **17a,** (*R*)-MTPA **17b** was synthesized from propargyl alcohol **16** (1.8 mg, 5.4 μmol) with (*S*)-MTPACl (2 μL, 10 μmol) in 87% yield: colorless oil; $^1$H NMR (400 MHz, CD$_3$OD): $\delta$=0.085 (6H, s, C*H*$_3$ of TBS), 0.924 (9H, s, *t*Bu of TBS), 0.945 (3H, t, $J$=7.3 Hz, CH$_2$-C*H*$_3$), 2.048 (2H, dq, $J$=7.3 Hz, C*H*$_2$-CH$_3$), 2.603 (1H, dd, $J$=14.6, 6.9 Hz, C*H*$_A$H$_B$-CHOMTPA), 2.678 (1H, dd, $J$=15.1, 7.3 Hz, CH$_A$*H*$_B$-CHOMTPA), 2.795 (1H, dd, $J$=7.3, 7.3 Hz, C=CH-C*H*$_2$-CH=C), 3.531 (3H, s, OMe), 4.250 (2H, dd, $J$=4.1, 2.3 Hz, C*H*$_2$-OTBS), 5.267 (1H, dtt, $J$=11, 7.3, 1.8 Hz, C*H*=CH-CH$_2$CH$_3$), 5.33–5.48 (2H, m, MTPAOCHCH$_2$-C*H*=CH, CH=C*H*-CH$_2$CH$_3$), 5.549 (1H, dt, $J$=11, 7.3 Hz, MTPAOCHCH$_2$-CH=C*H*-), 5.648 (1H, td, $J$=7.3, 1.4 Hz, C*H*-OMTPA), 5.749 (1H, ddt, $J$=16, 2.3, 2.3 Hz, TBSOCH$_2$-CH=C*H*), 6.222 (1H, ddd, $J$=16, 4.6 Hz, TBSOCH$_2$-C*H*=CH), 7.36–7.43 (3H, m, aromatic *H*), 7.48–7.53 ppm (2H, m, aromatic *H*).

**Preparation of activated zinc:**[23c] Nitrogen gas was bubbled through a suspension of Zn (12.0 g, 18.3 mmol) in H$_2$O (60 mL) for 30 min. Cu(OAc)$_2$·2H$_2$O (1.13 g, 6.24 mmol) was added to the suspension, and the resulting mixture was stirred for 30 min. Then AgNO$_3$ (1.24 g, 7.34 mmol) was added and the resulting mixture was stirred for 1 h. The suspension was filtered through a pad of Celite and the cake was washed with H$_2$O (2×25 mL), MeOH (2×25 mL), acetone (2×25 mL), and Et$_2$O (2×25 mL), and suspended in a mixture of H$_2$O/MeOH (1:1, 30 mL).

**Allylic alcohol 18**: A solution of **16** (500 mg, 1.49 mmol) in MeOH (5 mL) was added to a suspension of the activated Zn in a mixture of H$_2$O/MeOH (1:1, 10 mL). After being stirred at room temperature for 22 h, the reaction mixture was filtered through a pad of Celite and the cake was washed with a mixture of hexane/EtOAc (1:1). The filtrate was separated and the organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 20:1) to afford **18** (470 mg, 1.39 mmol) in 94% yield: yellow oil; $[\alpha]_D^{25}=-42$ ($c$=0.68, CHCl$_3$); IR (neat): $\tilde{\nu}$=3360, 2957, 2930, 2857, 1463, 1255, 1049 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=0.07 (6H, s, C*H*$_3$ of TBS), 0.91 (9H, s, *t*Bu of TBS), 0.96 (3H, t, $J$=7.5 Hz, CH$_2$-C*H*$_3$), 2.06 (2H, dq, $J$=7.4, 7.4 Hz, C*H*$_2$-CH$_3$), 2.26 (1H, ddd, $J$=14.4, 6.9, 6.9 Hz, HOCH-C*H*$_A$H$_B$-), 2.42 (1H, ddd, $J$=14.4, 6.9, 6.9 Hz, HOCH-CH$_A$*H*$_B$-), 2.80 (2H, dd, $J$=6.9, 6.9 Hz, C=CH-C*H*$_2$-CH=C), 4.22 (2H, dd, $J$=4.6, 1.2 Hz, C*H*$_2$-OTBS), 4.61 (1H, dt, $J$=8.1, 6.9 Hz, C*H*-OH), 5.25–5.31 (1H, m, CH=C*H*-CH$_2$-CH=CH), 5.36–5.42 (3H, m, CH=C*H*-CHOH, C*H*=CH-CH$_2$-CH=C*H*), 5.50–5.55 (1H, m, CH=CH-CH$_2$-C*H*=CH), 5.80 (1H, dt, $J$=14.9, 4.6 Hz, CH=C*H*-CH$_2$OTBS), 6.07 (1H, dd, $J$=10.9, 10.9 Hz, CH=C*H*-CH=CH-CH$_2$OTBS), 6.50–6.55 ppm (1H, m, C*H*=CH-CH$_2$OTBS); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=−5.3, 14.2, 18.4, 20.5, 25.7, 25.9, 35.3, 63.3, 67.6, 124.3, 124.5, 126.8, 129.6, 131.5, 132.1, 132.4, 134.9 ppm; HRMS (FAB) calcd for C$_{20}$H$_{36}$O$_2$SiCs 469.1539 [*M*+Cs]$^+$, found 469.1542.

**Bis-TBS ether 19:** TBSOTf (440 μL, 2.50 mmol) was added to a solution of **18** (420 mg, 1.25 mmol) and Et$_3$N (700 μL, 70 mmol) in CH$_2$Cl$_2$ (12.5 mL) at −78°C. After being stirred at −78°C for 10 min and then warmed to room temperature for 2 h, the reaction mixture was poured into ice-cold water. The resulting solution was extracted twice with EtOAc. Combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 40:1) to afford **19** (515 mg, 1.14 mmol) in 91% yield: colorless oil; $[\alpha]_D^{28}=-2.8$ ($c$=0.77, CHCl$_3$); IR (neat): $\tilde{\nu}$=2956, 2929, 2857, 1471, 1254, 1077 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=0.02 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.075 (3H, s, C*H*$_3$ of TBS), 0.079 (3H, s, C*H*$_3$ of TBS), 0.87 (9H, s, *t*Bu of TBS), 0.92 (9H, s, *t*Bu of TBS), 0.96 (3H, t, $J$=7.5 Hz, CH$_2$-C*H*$_3$), 2.06 (2H, dq, $J$=7.5, 7.5 Hz, C*H*$_2$-CH$_3$), 2.20 (1H, dt, $J$=13.7, 6.3 Hz, TBSOCH-C*H*$_A$H$_B$-), 2.35 (1H, dt, $J$=13.7, 6.9 Hz, TBSOCH-CH$_A$*H*$_B$-), 2.77 (2H, t, $J$=6.9 Hz, C=CH-C*H*$_2$-CH=C), 4.24 (2H, dd, $J$=4.6, 1.2 Hz, C*H*$_2$-OTBS), 4.58 (1H, dt, $J$=8.6, 6.9 Hz, C*H*OTBS), 5.26–5.43 (5H, m, CH=C*H*-CHOTBS, C*H*=C*H*-CH$_2$-C*H*=C*H*), 5.76 (1H, dt, $J$=14.9, 4.6 Hz, CH=C*H*-CH$_2$OTBS), 5.96 (1H, dd, $J$=11.5, 11.5 Hz, CH=C*H*-CH=CH-CH$_2$OTBS), 6.45–6.51 ppm (1H, m, C*H*=CH-CH$_2$OTBS); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=−5.2, −4.8, −4.4, 14.3, 18.2, 18.4, 20.5, 25.8, 25.9, 36.4, 63.3, 68.8, 124.4, 125.5, 127.1, 127.2, 129.9, 131.9, 134.0, 134.4 ppm; HRMS (FAB) calcd for C$_{26}$H$_{51}$O$_2$Si$_2$ 451.3428 [*M*+H]$^+$, found 451.3409.

**Alcohol 20:** TBAF (1.0 M in THF, 4.2 mL, 4.2 mmol) was added to a solution of **19** (474 mg, 1.05 mmol) in THF (10 mL) at −10°C. After being stirred for 50 min, the reaction mixture was quenched with saturated aqueous NH$_4$Cl. The resulting solution was extracted twice with EtOAc. Combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 20:1) to afford **20** (324 mg, 0.96 mmol) in 92% yield: colorless oil; $[\alpha]_D^{18}=+5.6$ ($c$=0.41, CHCl$_3$); IR (neat): $\tilde{\nu}$=3308, 2957, 2929, 1254, 1081 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=0.02 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.87 (9H, s, *t*Bu of TBS), 0.96 (3H, t, $J$=7.5 Hz, CH$_2$-C*H*$_3$), 2.06 (2H, br dq, $J$=6.9, 6.9, C*H*$_2$-CH$_3$), 2.21 (1H, ddd, $J$=13.7, 6.3, 6.3 Hz, TBSOCH-C*H*$_A$H$_B$-), 2.35 (1H, ddd, $J$=13.8, 6.9, 6.9 Hz, TBSOCH-CH$_A$*H*$_B$-), 2.77 (2H, dd, $J$=6.9, 6.9 Hz, C=CH-C*H*$_2$-CH=C), 4.21 (2H, br s, C*H*$_2$OH), 4.57 (1H, dt, $J$=8.6, 6.9 Hz, C*H*OTBS), 5.27–5.45 (5H, m, CH=C*H*-CHOTBS, C*H*=C*H*-CH$_2$-C*H*=C*H*), 5.83 (1H, dt, $J$=14.9, 5.8 Hz, CH=C*H*-CH$_2$OH), 5.95 (1H, dd, $J$=11.5, 11.5 Hz, CH=C*H*-CH=CH-CH$_2$OH), 6.47 ppm (1H, ddd, $J$=14.9, 11.5, 1.1 Hz, CH=CH-C*H*=CH-CH$_2$OH); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=−4.7, −4.3, 14.3, 18.2, 20.5, 25.7, 25.8, 36.3, 63.3, 68.8, 125.4, 126.2, 126.8, 127.1, 130.0, 131.9, 133.3, 135.4 ppm; HRMS (FAB) calcd for C$_{20}$H$_{36}$O$_2$SiCs 469.1539 [*M*+Cs]$^+$, found 469.1531.

**Sulfide 21**: A mixture of 2-mercaptobenzthiazole (58 mg, 0.35 mmol), Ph$_3$P (121 mg, 0.46 mmol), and **20** (78 mg, 0.23 mmol) in THF (2.3 mL) was stirred at room temperature for 5 min, and then DIAD (1.9 M toluene, 240 μL, 0.46 mmol) was added. After being stirred for 1 h at room temperature, the reaction mixture was poured into ice-cold water. The resulting solution was extracted twice with EtOAc. Combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 20:1) to afford **21** (104 mg, 0.21 mmol) in 93% yield: colorless oil; $[\alpha]_D^{22}=-2.4$ ($c$=0.55, CHCl$_3$); IR (neat): $\tilde{\nu}$=2956, 2928, 1461, 1428, 1254, 1077, 996 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=0.00 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.88 (9H, s, *t*Bu of TBS), 0.99 (3H, t, $J$=7.5 Hz, CH$_2$-C*H*$_3$), 2.08 (2H, dq, $J$=7.5, 7.5 Hz, C*H*$_2$-CH$_3$), 2.22 (1H, ddd, $J$=13.2, 6.3, 6.3 Hz, TBSOCH-C*H*$_A$H$_B$-), 2.35 (1H, ddd, $J$=13.2, 6.9, 6.9 Hz, TBSOCH-CH$_A$*H*$_B$-), 2.78 (2H, dd, $J$=6.9, 6.9 Hz, C=CH-C*H*$_2$-CH=C), 4.07 (1H, dd, $J$=14.3, 7.5 Hz, C*H*$_A$H$_B$-S-), 4.11 (1H, dd, $J$=14.3, 7.5 Hz, CH$_A$*H*$_B$-S-), 4.56 (1H, dt, $J$=8.0, 6.9 Hz, C*H*OTBS), 5.27–5.45 (5H, m, CH=C*H*-CHOTBS, C*H*=C*H*-CH$_2$-C*H*=C*H*), 5.88 (1H, dt, $J$=14.9, 7.5 Hz, CH=C*H*-CH$_2$-S-), 5.95 (1H, dd, $J$=11.5, 11.5 Hz, CH=C*H*-CH=CH-CH$_2$-S-), 6.61 (1H, ddd, $J$=14.9, 11.5, 1.1 Hz C*H*=CH-CH$_2$-S-), 7.32 (1H, dd, $J$=8.0, 8.0 Hz, aromatic *H*), 7.44 (1H, dd, $J$=8.0, 8.0 Hz, aromatic *H*), 7.77 (1H, d, $J$=8.0 Hz, aromatic *H*), 7.90 ppm (1H, d, $J$=8.0 Hz, aromatic *H*); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=−4.8, −4.4, 14.3, 18.1, 20.6, 25.7, 25.8, 35.7, 36.3, 68.8, 120.9, 121.6, 124.3, 125.2, 126.0, 126.5, 127.1, 128.2, 129.5, 130.1, 131.9, 135.3, 135.8, 153.1, 166.0 ppm; HRMS (FAB) calcd for C$_{27}$H$_{40}$NOS$_2$Si 486.2321 [*M*+H]$^+$, found 486.2320.

**Sulfone 7**: H$_2$O$_2$ (30% in H$_2$O, 220 μL, 2.10 mmol) was added to a solution of **21** (104 mg, 0.21 mmol) and Mo$_7$(NH$_4$)$_6$O$_{24}$·4H$_2$O (79 mg, 64 μmol) in EtOH (4.2 mL) at room temperature. After being stirred for 3 h, the reaction mixture was cooled to 0°C, and saturated aqueous Na$_2$S$_2$O$_3$ was added to the mixture. The resulting mixture was extracted twice with EtOAc. Combined organic layers were washed with H$_2$O and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 20:1) to afford **7** (80 mg, 0.15 mmol) in 72% yield: off-white waxy solid; m.p. 53–55°C; $[\alpha]_D^{18}=-8.1$ ($c$=0.85, CHCl$_3$); IR (neat): $\tilde{\nu}$=2956, 2928, 2855, 1472, 1335, 1146, 1080 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=−0.18 (3H, s, C*H*$_3$ of TBS), −0.14 (3H, s, C*H*$_3$ of TBS), 0.78

  

(9H, s, *t*Bu of TBS), 0.96 (3H, t, $J=7.5$ Hz, $CH_2$-$CH_3$), 2.00–2.07 (3H, m, $CH_2$-$CH_3$, TBSOCH-$CH_AH_B$-), 2.18 (1H, dt, $J=14.3$, 6.9 Hz, TBSOCH-$CH_AH_B$-), 2.68 (2H, dd, $J=6.9$, 6.9 Hz, C=CH-$CH_2$-CH=C), 4.25–4.36 (3H, m, $CH_2$-$SO_2$-, CHOTBS), 5.13–5.40 (4H, m, CH=CH-$CH_2$-CH=CH), 5.42 (1H, dd, $J=10.9$, 9.2 Hz, CH=CH-CHOTBS), 5.67 (1H, dt, $J=15.5$, 8.0 Hz, CH=CH-$CH_2$-$SO_2$-), 5.89 (1H, dd, $J=11.5$, 10.9 Hz, CH=CH-CH=CH-$CH_2$-$SO_2$-), 6.45 (1H, dd, $J=15.5$, 11.5 Hz CH=CH-$CH_2$-$SO_2$-), 7.58 (1H, dd, $J=8.0$, 8.0 Hz, aromatic *H*), 7.63 (1H, dd, $J=8.0$, 8.0 Hz, aromatic *H*), 7.99 (1H, d, $J=8.0$ Hz, aromatic *H*), 8.23 ppm (1H, d, $J=8.0$ Hz, aromatic *H*); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-5.0$, −4.6, 14.3, 18.0, 20.5, 25.7, 36.0, 58.5, 68.6, 99.9, 117.7, 122.3, 124.8, 125.4, 125.8, 127.0, 127.7, 128.0, 130.2, 132.0, 135.4, 136.9, 137.9, 152.6, 165.3 ppm; HRMS (FAB) calcd for $C_{27}H_{40}NO_3S_2Si$ 518.2219 $[M+H]^+$, found 518.2225.

**Triene (7*R*,8*E*)-22:** $P_4$-*t*Bu (1.0 M in hexane, 70 μL, 70 μmol) was added to the mixture of **7** (30 mg, 58 μmol) and the crude (*R*)-**4** (35 mg) in $CH_3CN$ (2.3 mL) at −40 °C. The mixture was stirred for 5 min at −40 °C, and then allowed to warm to room temperature for 2 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the resulting solution was extracted with $Et_2O$. The organic layer was washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 100:0 to 40:1) to afford (7*R*)-**22** along with other stereoisomers (20 mg, 32 μmol) in 56% yield. The mixture was further purified by HPLC (Inertsil, SIL 100 A, 250×10 mm, UV 254 nm, hexane/EtOAc 95:5, 3.0 mL min$^{-1}$) to give (7*R*,8*E*)-**22** (8.3 mg, 0.013 mmol, $t_R=17.2$ min) in 22% yield and (7*R*,8*Z*)-**22** (5.1 mg, 8.3 μmol, $t_R=14.5$ min) in 14% yield: (7*R*,8*E*)-**22**: $[\alpha]_D^{17}=-15$ ($c=0.42$, $CHCl_3$); IR (neat): $\tilde{\nu}=2955$, 2929, 2856, 1472, 1254, 1073 cm$^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$): $\delta=0.09$ (3H, s, $CH_3$ of TBS), 0.10 (3H, s, $CH_3$ of TBS), 0.12 (6H, s, $CH_3$ of TBS), 0.93 (3H, t, $J=7.3$ Hz, H-22), 1.01 (18H, s, *t*Bu of TBS), 1.81 (2H, td, $J=7.8$, 5.0 Hz, H-2), 2.03 (2H, br dq, $J=6.8$, 6.8 Hz, H-21), 2.25–2.60 (6H, m, H-3, H-6, and H-15), 2.85 (2H, dd, $J=5.5$, 5.5 Hz, H-18), 3.35–3.42 (2H, m, $OCH_AH_BCH_AH_BO$), 3.49–3.56 (2H, m, $OCH_AH_BCH_AH_BO$), 4.20 (1H, dt, $J=6.4$, 6.4 Hz, H-7), 4.74 (1H, dt, $J=7.8$, 6.9 Hz, H-14), 4.84 (1H, t, $J=5.0$ Hz, H-1), 5.39–5.65 (7H, m, H-4, H-5, H-13, H-16, H-17, H-19, and H-20), 5.71 (1H, dd, $J=15.6$, 6.4 Hz, H-8), 5.97 (1H, dd, $J=11.4$, 11.4 Hz, H-12), 6.14 (1H, dd, $J=14.6$, 11.0 Hz, H-10), 6.35 (1H, dd, $J=15.1$, 11.0 Hz, H-9), 6.63 ppm (1H, dd, $J=14.6$, 11.9 Hz, H-11); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-4.8$, −4.4, 14.3, 18.2, 18.3, 20.6, 22.1, 25.7, 25.8, 25.9, 33.7, 36.2, 36.4, 64.9, 69.0, 72.9, 104.1, 125.5, 126.0, 127.1, 127.3, 127.8, 129.3, 129.9, 130.6, 131.9, 133.5, 134.9, 137.5 ppm; HRMS (EI) calcd for $C_{36}H_{64}O_4Si_2$ 616.4343 $[M]^+$, found 616.4352. (7*R*,8*Z*)-**22**: $[\alpha]_D^{26}=-5.7$ ($c=0.090$, $CHCl_3$); IR (neat): $\tilde{\nu}=2956$, 2928, 2856, 1462, 1254, 1074 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): $\delta=0.10$ (3H, s, $CH_3$ of TBS), 0.11 (3H, s, $CH_3$ of TBS), 0.12 (3H, s, $CH_3$ of TBS), 0.13 (3H, s, $CH_3$ of TBS), 0.92 (3H, t, $J=7.5$ Hz, H-22), 1.006 (9H, s, *t*Bu of TBS), 1.009 (9H, s, *t*Bu of TBS), 1.81 (2H, td, $J=8.0$, 5.0 Hz, H-2), 2.02 (2H, qd, $J=7.5$, 5.7 Hz, H-21), 2.26–2.55 (6H, m, H-3, H-6 and H-15), 2.84 (2H, dd, $J=6.3$, 6.3 Hz, H-18), 3.36–3.42 (2H, m, $OCH_AH_BCH_AH_BO$), 3.52–3.56 (2H, m, $OCH_AH_BCH_AH_BO$), 4.72 (1H, dt, $J=7.5$, 7.5 Hz, H-7 or H-14), 4.73 (1H, dt, $J=7.4$, 7.4 Hz, H-7 or H-14), 4.84 (1H, t, $J=5.0$ Hz, H-1), 5.42–5.65 (8H, m, H-4, H-5, H-8, H-13, H-16, H-17, H-19, and H-20), 5.99 (1H, dd, $J=11.4$, 11.4 Hz, H-9 or H-12), 6.04 (1H, dd, $J=11.4$, 11.4 Hz, H-9 or H-12), 6.59 (1H, dd, $J=14.9$, 11.4 Hz, H-10 or H-11), 6.64 ppm (1H, dd, $J=14.9$, 11.4 Hz, H-10 or H-11); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$, −4.3, 14.3, 18.2, 20.6, 22.2, 25.78, 25.84, 25.9, 29.7, 33.7, 36.3, 36.4, 64.9, 69.03, 69.04, 104.1, 125.5, 126.0, 127.1, 127.65, 127.69, 128.8, 128.9, 130.0, 130.6, 131.9, 135.7, 135.8 ppm; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4241 $[M+Na]^+$, found 639.4244.

**Carboxylic acid (7*R*)-23:** TMSOTf (37 μL, 0.20 mmol) was added to a solution of (7*R*)-**22** (8.3 mg, 14 μmol) and 2,6-lutidine (35 μL, 0.30 mmol) in $CH_2Cl_2$ (1.3 mL) at −20 °C. After 1 h at −20 °C, $H_2O$ was added to the reaction mixture. The solution was stirred at room temperature for an additional 1 h, and diluted with $CH_2Cl_2$. The separated organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated to give the crude aldehyde, which was used for the next reaction without further purification. A solution of $NaClO_2$ (11 mg, 0.12 mmol) and $NaH_2PO_4{\cdot}4H_2O$ (20 mg, 0.13 mmol) in $H_2O$ (0.6 mL) was added to a solution of the crude aldehyde in a mixture of 2-methyl-2-butene (0.6 mL) and *t*BuOH (0.6 mL) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with $H_2O$ (2 mL) and EtOAc (5 mL). The separated organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc/AcOH 10:0:0 to 20:1:0 to 10:1:0.01) to afford (7*R*)-**23** (6.0 mg, 0.010 mmol) in 76% yield over 2 steps: a colorless oil; $[\alpha]_D^{20}=-15$ ($c=0.27$, $CHCl_3$); IR (neat): $\tilde{\nu}=2929$, 2856, 1712, 1254, 1076 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): $\delta=0.090$ (3H, s, $CH_3$ of TBS), 0.093 (3H, s, $CH_3$ of TBS), 0.12 (3H, s, $CH_3$ of TBS), 0.13 (3H, s, $CH_3$ of TBS), 0.93 (3H, t, $J=7.3$ Hz, H-22), 1.007 (9H, s, *t*Bu of TBS), 1.013 (9H, s, *t*Bu of TBS), 2.03 (2H, qd, $J=7.3$, 5.5 Hz, H-21), 2.09 (2H, t, $J=7.3$ Hz, H-2), 2.20–2.60 (6H, m, H-3, H-6, and H-15), 2.85 (2H, dd, $J=5.5$, 5.5 Hz, H-18), 4.17 (1H, dt, $J=5.9$, 5.9 Hz, H-7), 4.74 (1H, br dt, $J=8.2$, 8.2 Hz, H-14), 5.30–5.63 (7H, m, H-4, H-5, H-13, H-16, H-17, H-19 and H-20), 5.68 (1H, dd, $J=15.1$, 6.4 Hz, H-8), 5.98 (1H, dd, $J=11.4$, 11.4 Hz, H-12), 6.15 (1H, dd, $J=14.7$, 11.0 Hz, H-10), 6.34 (1H, dd, $J=15.6$, 11.0 Hz, H-9), 6.65 ppm (1H, dd, $J=15.1$, 11.4 Hz, H-11); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-4.78$, −4.4, −4.3, 14.3, 18.2, 18.3, 20.6, 22.7, 25.7, 25.8, 25.9, 33.6, 36.2, 36.4, 69.0, 72.8, 125.5, 127.2, 127.4, 127.15, 127.14, 127.7, 129.0, 129.4, 129.9, 131.9, 133.4, 135.0, 137.3, 177.7 ppm; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3952 $[M-H]^-$, found 587.3947.

**7*R*,14*S*-dihydroxydocosa-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid (7*R*)-1**: TBAF (1.0 M in THF, 0.09 mL, 90 μmol) was added to a solution of (7*R*)-**23** (5.3 mg, 9.0 μmol) in THF (0.9 mL) at 0 °C. After being stirred at room temperature for 11 h, the reaction mixture was quenched with saturated aqueous $NH_4Cl$. The resulting solution was extracted with $Et_2O$. The organic layer was washed with aqueous HCl (0.1 N), $H_2O$, and brine, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc/AcOH 1:1:0 to 1:5:0.01) to afford (7*R*)-**1** (3.8 mg, 0.011 mmol) in 99% yield: pale yellow oil; HPLC analysis: L-column2 ODS (CERI) (3 μm, 4.6×150 mm), UV 270 nm, 1.0 mL min$^{-1}$, $KH_2PO_4$ buffer (pH 3.0, 25 mM)/$CH_3CN$ 55:45, $t_R=12.4$ min; $[\alpha]_D^{22}=-31$ ($c=0.19$, MeOH); IR (neat): $\tilde{\nu}=3327$, 2923, 1713, 1399, 1264, 996 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3OD$): $\delta=0.96$ (3H, t, $J=7.5$ Hz, H-22), 2.07 (2H, dq, $J=7.5$, 7.5 Hz, H-21), 2.19–2.42 (8H, m, H-2, H-3, H-6, and H-15), 2.79 (2H, dd, $J=6.9$, 6.9 Hz, H-18), 4.12 (1H, dt, $J=6.9$, 5.2 Hz, H-7), 4.57 (1H, dt, $J=9.8$, 7.4 Hz, H-14), 5.26–5.47 (7H, m, H-4, H-5, H-13, H-16, H-17, H-19 and H-20), 5.75 (1H, dd, $J=14.9$, 6.9 Hz, H-8), 6.07 (1H, dd, $J=11.4$, 11.4 Hz, H-12), 6.24 (1H, dd, $J=14.3$, 10.9 Hz, H-10), 6.28 (1H, dd, $J=14.9$, 10.9, 1.1 Hz, H-9), 6.51 ppm (1H, br dd, $J=13.8$, 12.0, Hz, H-11); $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta=14.7$, 21.5, 24.1, 26.6, 34.9, 36.2, 36.5, 68.5, 73.0, 126.1, 127.5, 128.2, 128.9, 130.6, 131.1, 131.3, 131.4, 132.8, 134.8, 135.0, 138.0, 177.1 ppm; HRMS (FAB) calcd for $C_{22}H_{31}O_4$ 359.2222 $[M-H]^-$, found 359.2220.

**Triene (7*S*,8*E*)-22:** Following the same procedure for synthesis of triene (7*R*,8*E*)-**22**, triene (7*S*,8*E*)-**22** (4.1 mg, 6.6 μmol) and (7*S*,8*Z*)-**22** were synthesized from **7** (15 mg, 29 μmol) and the crude (*S*)-**4** in 63% combined yield. The obtained compounds were further purified by using the same HPLC procedure for (7*R*)-**22**. ((7*S*,8*Z*)-**22**: $t_R=14.7$ min (23% yield), (7*S*,8*E*)-**22**: $t_R=13.0$ min (18% yield)): (7*S*,8*E*)-**22**: $[\alpha]_D^{17}=+18$ ($c=0.40$, $CHCl_3$); IR (neat): $\tilde{\nu}=2955$, 2928, 2856, 1471, 1254, 1069 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): $\delta=0.09$ (3H, s, $CH_3$ of TBS), 0.10 (3H, s, $CH_3$ of TBS), 0.13 (3H, s, $CH_3$ of TBS), 0.14 (3H, s, $CH_3$ of TBS), 0.93 (3H, t, $J=7.4$ Hz, H-22), 1.01 (18H, s, *t*Bu of TBS), 1.79–1.83 (2H, m, H-2), 2.02 (2H, dq, $J=7.5$ Hz, H-21), 2.28–2.54 (6H, m, H-3, H-6 and H-15), 2.84 (2H, dd, $J=5.8$, 5.8 Hz, H-18), 3.35–3.41 (2H, m, $OCH_AH_BCH_AH_BO$), 3.50–3.57 (2H, m, $OCH_AH_BCH_AH_BO$), 4.19 (1H, dt, $J=6.3$, 6.3 Hz, H-7), 4.73 (1H, dt, $J=8.0$, 6.9 Hz, H-14), 4.83 (1H, t, $J=5.2$ Hz, H-1), 5.40–5.64 (7H, m, H-4, H-5, H-13, H-16, H-17, H-19 and H-20), 5.70 (1H, dd, $J=15.5$, 6.3 Hz, H-8), 5.96 (1H, dd, $J=11.4$, 11.4 Hz, H-12), 6.13 (1H, dd, $J=14.9$, 10.9 Hz, H-10), 6.34 (1H, dd, $J=15.5$, 10.9 Hz, H-9), 6.63 ppm (1H, dd, $J=14.3$, 11.4 Hz, H-11); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=-4.8$, −4.4, −4.3, 14.3, 18.2, 18.3, 20.6, 22.1, 25.7, 25.8, 25.9, 33.7, 36.2, 36.4, 64.9, 68.9, 72.9, 104.1, 125.5, 126.0, 127.1, 127.3, 127.8, 129.3, 130.0, 130.5, 131.9, 133.4, 134.9, 137.4 ppm; HRMS (FAB) calcd for $C_{36}H_{64}O_4Si_2Cs$ 749.3398 $[M+Cs]^+$, found 749.3392. (7*S*,8*Z*)-**22**: $[\alpha]_D^{26}=+27$ ($c=0.13$, $CHCl_3$); IR (neat): $\tilde{\nu}=2956$, 2929, 2856, 1472, 1256, 1073,

  

836 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): $\delta = 0.08$ (3H, s, $CH_3$ of TBS), 0.10 (3H, s, $CH_3$ of TBS), 0.13 (6H, s, $CH_3$ of TBS), 0.92 (3H, t, $J = 7.5$ Hz, H-22), 1.00 (9H, s, *t*Bu of TBS), 1.01 (9H, s, *t*Bu of TBS), 1.81 (2H, td, $J = 7.5$, 4.5 Hz, H-2), 2.02 (2H, qd, $J = 7.5$, 5.0 Hz, H-21), 2.25–2.55 (6H, m, H-3, H-6 and H-15), 2.84 (2H, dd, $J = 6.5$, 6.5 Hz, H-18), 3.36–3.42 (2H, m, $OCH_AH_BCH_AH_BO$), 3.50–3.58 (2H, m, $OCH_AH_BCH_AH_BO$), 4.72 (1H, dt, $J = 7.0$, 7.0 Hz, H-7 or H-14), 4.73 (1H, dt, $J = 7.0$, 7.0 Hz, H-7 or H-14), 4.84 (1H, t, $J = 4.5$ Hz, H-1), 5.38–5.63 (8H, m, H-4, H-5, H-8, H-13, H-16, H-17, H-19 and H-20), 5.98 (1H, dd, $J = 10.5$, 10.5 Hz, H-9 or H12), 6.04 (1H, dd, $J = 10.5$, 10.5 Hz, H-9 or H12), 6.59 (1H, dd, $J = 15.0$, 11.0 Hz, H-10 or H-11), 6.64 ppm (1H, dd, $J = 14.5$, 10.0 Hz, H-10 or H-11); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, −4.4, −4.3, 14.3, 18.2, 20.6, 22.2, 25.78, 25.84, 25.9, 29.7, 33.7, 36.3, 36.4, 64.9, 68.98, 69.01, 104.1, 125.5, 126.0, 127.1, 127.67, 127.73, 128.8, 128.9, 130.0, 130.6, 131.9, 135.7, 135.8 ppm; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4241 $[M+Na]^+$, found 639.4231.

**Carboxylic acid (7*S*)-23:** Following the same procedure for synthesis of (7*R*)-**23**, (7*S*)-**23** (5.9 mg, 10 μmol) was synthesized from (7*S*,8*E*)-**22** (8.0 mg, 13.0 μmol) in 77% yield over 2 steps: $[\alpha]_D^{20} = +16$ ($c = 0.30$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2956$, 2928, 2856, 1712, 1471, 1254, 1076 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): $\delta = 0.09$ (3H, s, $CH_3$ of TBS), 0.10 (3H, s, $CH_3$ of TBS), 0.13 (3H, s, $CH_3$ of TBS), 0.14 (3H, s, $CH_3$ of TBS), 0.94 (3H, t, $J = 7.5$ Hz, H-22), 1.01 (9H, s, *t*Bu of TBS), 1.02 (9H, s, *t*Bu of TBS), 2.00–2.06 (2H, m, H-21), 2.10 (2H, t, $J = 7.5$ Hz, H-2), 2.19–2.40 (5H, m, H-3, H-6, and H-15a), 2.52 (1H, ddd. $J = 14.3$, 6.9, 6.9 Hz, H-15b), 2.84 (2H, dd, $J = 6.3$, 6.3 Hz, H-18), 4.16 (1H, dt, $J = 6.3$, 6.3 Hz, H-7), 4.74 (1H, dt, $J = 8.6$, 6.9 Hz, H-14), 5.32–5.37 (1H, m, H-4), 5.40–5.47 (2H, m, H-19 and H-20), 5.49–5.62 (4H, m, H-5, H-13, H-16 and H-17), 5.68 (1H, dd, $J = 15.5$, 6.5 Hz, H-8), 5.98 (1H, dd, $J = 11.5$, 11.5 Hz, H-12), 6.15 (1H, dd, $J = 14.9$, 11.5 Hz, H-10), 6.34 (1H, dd, $J = 15.5$, 11.5 Hz, H-9), 6.65 ppm (1H, dd, $J = 14.9$, 12.0 Hz, H-11); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = -4.8$, −4.4, −4.3, 14.3, 18.2, 18.3, 20.6, 22.7, 25.7, 25.8, 25.9, 33.7, 36.2, 36.3, 68.9, 72.8, 125.5, 127.1, 127.2, 127.5, 127.8, 128.9, 129.5, 130.0, 131.9, 133.3, 135.0, 137.2, 178.0 ppm; HRMS (FAB) calcd for $C_{34}H_{59}O_4Si_2$ 587.3952 $[M-H]^-$, found 587.3947.

**7*S*,14*S*-dihydroxydocosa-4*Z*,8*E*,10*E*,12*Z*,1*Z*,19*Z*-hexaenoic acid (7*S*)-1**: Following the same procedure for synthesis of (7*R*)-**1**, (7*S*)-**1** (3.5 mg, 9.7 μmol) was synthesized from (7*S*)-**23** (5.9 mg, 10 μmol) in 97% yield: colorless oil; HPLC analysis: L-column2 ODS (CERI) (3 μm, 4.6 × 150 mm), UV 270 nm, 1.0 mL $min^{-1}$, 25 mM $KH_2PO_4$ buffer (pH 3.0)/$CH_3CN$ 55:45, $t_R = 11.6$ min; $[\alpha]_D^{22} = -23$ ($c = 0.18$, MeOH); IR (neat): $\tilde{\nu} =$ 3304, 3011, 2962, 2923, 1713, 1400, 1264, 996 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$): $\delta = 0.96$ (3H, t, $J = 7.5$ Hz, H-22), 2.08 (2H, dq, $J = 7.5$, 7.5 Hz, H-21), 2.19–2.42 (8H, m, H-2, H-3, H-6, and H-15), 2.79 (2H, dd, $J = 6.9$, 6.9 Hz, H-18), 4.12 (2H, dt, $J = 6.9$, 6.3 Hz, H-7), 4.57 (1H, dt, $J = 8.6$, 6.9 Hz, H-14), 5.26–5.47 (7H, m, H-4, H-5, H-13, H-16, H-17, H-19 and H-20), 5.75 (1H, dd, $J = 14.9$, 6.9 Hz, H-8), 6.07 (1H, dd, $J = 11.5$, 11.5 Hz, H-12), 6.24 (1H, dd, $J = 14.3$, 10.9 Hz, H-10), 6.28 (1H, dd, $J =$ 14.9, 10.9, 1.2 Hz, H-9), 6.51 ppm (1H, br dd, $J = 13.8$, 11.5, Hz, H-11); $^{13}C$ NMR (125 MHz, $CD_3OD$): $\delta = 14.7$, 21.5, 24.2, 26.6, 35.2, 36.2, 36.5, 68.5, 73.0, 126.1, 127.4, 128.2, 128.9, 130.6, 131.2, 131.3, 131.4, 132.8, 134.8, 135.0, 138.0, 178.6 ppm; HRMS (FAB) calcd for $C_{22}H_{31}O_4$ 359.2222 [M−H], found 359.2227.

**Bioassay**: Murine peritonitis was carried out by using 7- to 8-week year old C57BL/6 male mice (CLEA Japan). Maresin or vehicle alone was injected into the tail vein, followed by 1 mL of zymosan A (1 mg $mL^{-1}$; Sigma–Aldrich) injected into the peritoneum. After 2 h, peritoneal lavages were collected and the cells were enumerated with light microscopy.

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