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ARTICLE

Stereoselective ozonolysis of TMS-substituted allylic alcohol derivatives and synthesis of 14*R*,15*S*- and 14*S*,15*S*-diHETE†

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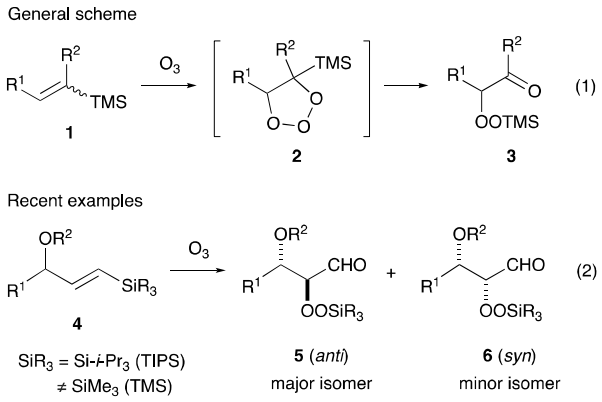
Ozonolysis of an TMS-substituted olefins produces α-carbonyl TMS peroxides without cleavage of the C=C bond. Herein, stereochemistry in the ozonolysis was studied using silyl derivatives of (*E*)- and (*Z*)-(1-TMS)alk-1-en-3-ols. The (*E*)-isomers afforded the *anti*-3-siloxy-2-(TMS-oxy)aldehydes as the major stereoisomer (*anti*/*syn* = 3–9:1) after reductive work-up with Ph_3P. In contrast, *Z*-olefins selectively gave the *syn* isomers with *syn*/*anti* ratios of 4–19:1. Facial selection was speculated based on the Cieplak effect. This ozonolysis was successfully applied for the synthesis of 14*R*,15*S*- and 14*S*,15*S*-diHETEs (*anti* and *syn* isomers, respectively) in enantioenriched.

Introduction

Since ozonolysis is an oxidation reaction that is employed to cleave a double bond to two carbonyl groups after reductive work-up, less attention has been paid to the stereochemical course.[1] In contrast, $SiMe_3$ (TMS)-substituted olefins **1** are converted into α-carbonyl TMS peroxides **3** without cleavage of the C=C bond (Scheme 1, eq 1).[2,3] In the synthesis of artemisinin[4] and its analogues,[5] O_3 was found to access the substituted (TMS-methylene)cyclohexane through the sterically less hindered side of the ring. Recently, ozonolysis of TMS ethers **4** with *i*-Pr_3Si (TIPS) as SiR_3 was demonstrated to produce *anti* peroxides **5** as the major products over the *syn* isomers (Scheme 1, eq 2), although the selectivity was highly dependent on the allylic substituent R^1.[6] According to the authors, substrates with TMS as SiR_3 were omitted from their investigation because of expected rapid hydrolysis[2] of the TMS peroxides. However, easy access to **4** (SiR_3 = TMS) in an enantio-enriched form by several methods[7] starting with TMS-acetylene[8] is a synthetic advantage. We confirmed this in the synthesis of resolvin E2.[9] Although the newly generated stereogenic center was destroyed during further transformation, without determination of the chirality and stereoselectivity, the TMS ether was found to be fairly stable. Herein, we present the stereoselective ozonolysis of (*E*)- and (*Z*)-TMS-substituted allylic alcohol derivatives and its application for the synthesis of 14,15-diHETE in *anti* and *syn* forms, wherein TMS acted as a protective group.



Scheme 1 Ozonolysis of silyl-substituted olefins.

Results and discussion

Olefins **9a–e** and **13a–e** possessing C_5H_{11}, Et, or *i*-Pr as R^1 and TBDMS, TES, or TBDPS as R^2 were chosen as substrates for ozonolysis (Scheme 2), and synthesized in good yields by a sequence of reactions: (1) addition of TMS-acetylene/*n*-BuLi to the aldehyde (R^1CHO); (2) reduction of the resulting propargylic alcohols **7a**,**b**,**c** by Red-Al[10] or semi-hydrogenation with P-2 nickel;[11] and (3) silylation of the hydroxyl groups with TBDMSCl, TESCl, or TBDPSCl. The olefins **9a–e** and **13a–e** were isolated in diastereomic ratios ≥91:9 *E*/*Z* and ≥94:6 *E*/*Z*, respectively. Later, **9a** and **13a** in enantioenriched forms were prepared for the synthesis of 14,15-diHETE.

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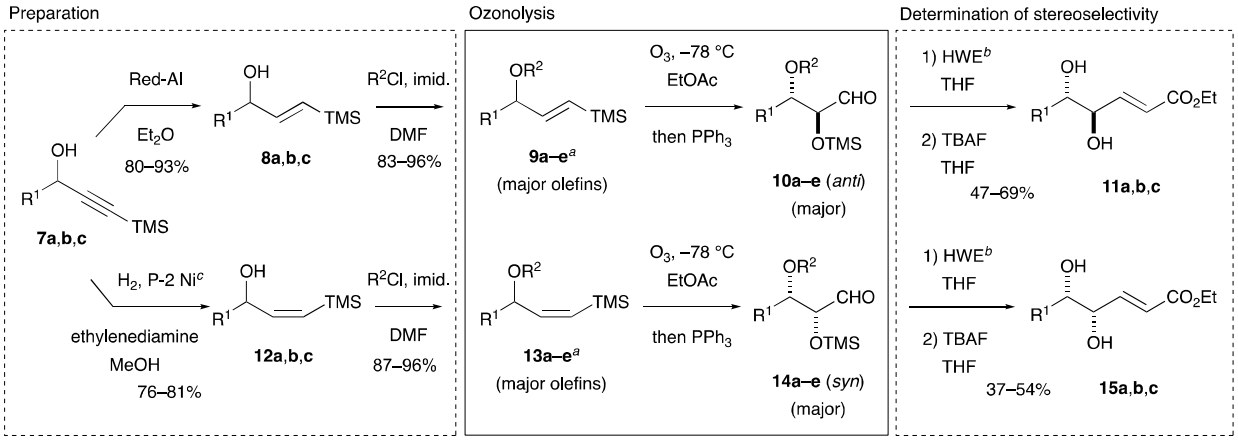

Scheme 2 Ozonolysis of allylic alcohol derivatives.
[a] **a**–**e**, see Table 1. [b] HWE: $(EtO)_2P(O)CH_2CO_2Et$, NaH. [c] Freshly prepared from $Ni(OAc)_2{\cdot}4H_2O$ and $NaBH_4$ (1:1).

Ozonolysis of *E*-olefin **9a** (*E*/*Z* = 94:6) was carried out at –78 °C in EtOAc, and reductive work-up with Ph_3P at rt for 20–30 min afforded a diastereomeric mixture of **10a** and **14a**. Me_2S did not reduce the peroxide, as confirmed from the unchanged ^1H NMR spectra of the products before and after the addition of Me_2S. As the signals of the isomers were overlapped in the ^1H NMR spectrum and the mixture was hardly separated by chromatography on silica gel, the crude aldehyde was subjected to Horner–Wadsworth–Emmons (HWE) reaction, followed by desilylation to afford a mixture of diols **11a** and **15a** in 81:19 ratio and 66% yield from **9a** over three steps (Table 1, entry 1). Since the olefinic purity of **9a** (over **13a**) was 94%, a ratio based on pure *E*-olefin **9a** was also given after correction. The observed and corrected ratios are considered to be practical and intrinsic, respectively. The TES and TBDPS ethers **9d** and **9e** produced diols **11a**/**15a** with slightly low ratios (entries 2 and 3). Substrate **9b** possessing the Et substituent produced diols **11b**/**15b** in 84:16 ratio, indicating stereoselectivity similar to that of **9a** (entry 4). Slightly better selectivity was provided by the isopropyl substrate **9c** (entry 5).

In contrast to the *E*-substrates, *Z*-isomers **13a**–**e** predominantly afforded *syn* isomers **15a**–**c** with slightly higher degrees of selectivity (entries 6–10).

The stereochemistry of the above products was determined as follows. The ^1H NMR spectrum of **15a** produced as a minor and a major isomers in entries 2 and 6 was consistent with the literature data for the *syn* isomer.[12] Furthermore, a mixture of **11a** and **15a** was converted into acetonides **16** and **17** with $MeC(OMe)_3$ and PPTS, which were separated by chromatography on silica gel (Fig. 1). The ^1H NMR spectrum of **17** was identical with that of the *syn* isomer in the literature.[12] The large and small differences (Δδ) in the chemical shifts of the acetonide Me signals of **16** and **17** in the ^1H and ^{13}C spectra were consistent the typical values for *anti* and *syn* isomers.[13] The ^{13}C NMR of *syn* diol **15b** possessing an Et group, as well as the ^1H and ^{13}C NMR spectra of *syn* diol **15c** possessing an *i*-Pr group, were coincident with the literature data.[14,15]

Table 1 Ozonolysis of TMS-allylic alcohol derivatives

Entry	R^1	R^2	Substrate	*E*/*Z*[a]	Major product	Yield (%)[b]	*anti*/*syn* Observed[a]	*anti*/*syn* Corrected[c]
1	C_5H_{11}	TBDMS	**9a**	94:6	**11a**	66	81:19	85:15
2	C_5H_{11}	TES	**9d**	93:7	**11a**	69	75:25	79:21
3	C_5H_{11}	TBDPS	**9e**	95:5	**11a**	55	73:27	76:24
4	Et	TBDMS	**9b**	94:6	**11b**	47	80:20	84:16
5	*i*-Pr	TBDMS	**9c**	91:9	**11c**	58	82:18	90:10
6	C_5H_{11}	TBDMS	**13a**	4:96	**15a**	49	16:84	13:87
7	C_5H_{11}	TES	**13d**	5:95	**15a**	54	21:79	18:82
8	C_5H_{11}	TBDPS	**13e**	5:95	**15a**	44	12:88	9:91
9	Et	TBDMS	**13b**	4:96	**15b**	44	16:84	13:87
10	*i*-Pr	TBDMS	**13c**	6:94	**15c**	37	10:90	5:95

[a] Ratios were determined by ^1H NMR spectroscopy unless otherwise noted. [b] Isolated yield. [c] Calculated based on the *E*/*Z* ratios of the substrates.

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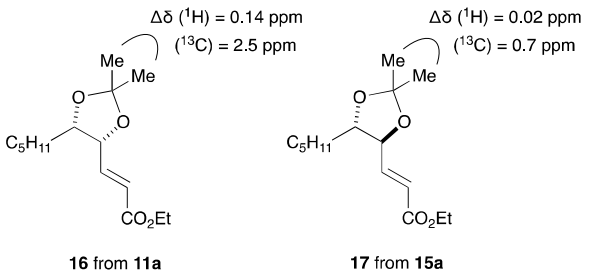
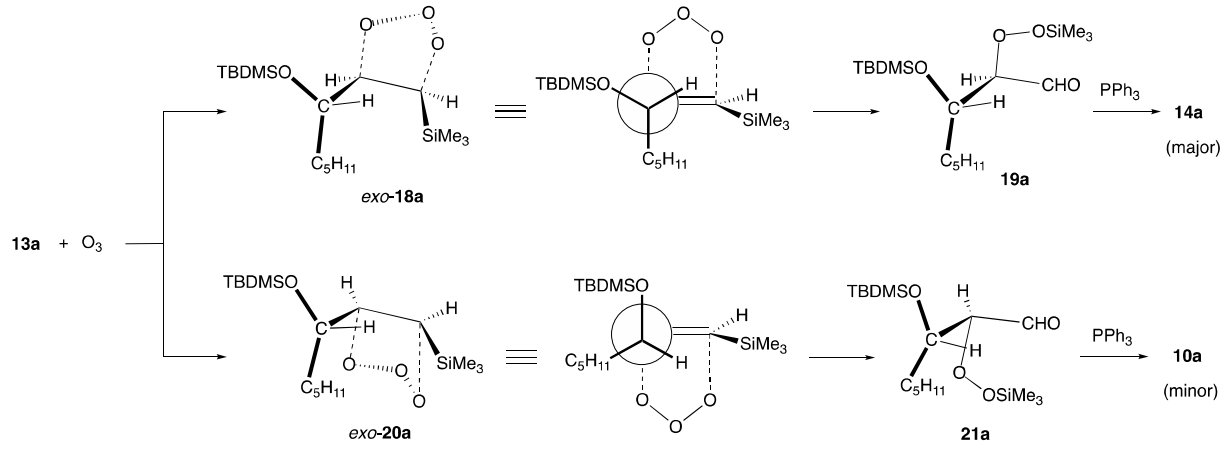


Fig. 1 Derivatization to acetonides for determination of the stereochemistry.

Scheme 3 describes the plausible steric course for the ozonolysis of the conformationally rigid *Z*-olefin **13a** on the basis of the Cieplak rule.[16] In this instance, the central oxygen atom of O_3 is located at the outside (*exo*) position[1] with respect to the allylic moiety, instead of the *endo* position (structures of the *endo*-TSs are not shown) because of minimizing steric repulsion toward **13a**. According to the Cieplak rule, the developing electron-deficient $\sigma^{\ddagger *}$ orbital between C_{olefin}–$O_{terminal}$ is stabilized by overlap with the neighbouring σ orbital ($C_{allylic}$–C_{pentyl} or $C_{allylic}$–O_{TBDMS}) that donate electron to the $\sigma^{\ddagger *}$ orbital. In general, the C–C bond has higher electron density than the C–O bond; hence, the orbital interaction between the incipient $\sigma^{\ddagger *}$ and the σ orbital of the C–C_{pentyl} bond is more preferable, and the reaction should selectively proceed via *exo*-**18a** to afford peroxide **19a**. The substrate **13c** possessing the *i*-Pr group instead of C_5H_{11} showed higher selectivity because of the increased steric bulkiness, which prevents the O_3 approach from the opposite *Si* face more effectively. A similar orbital interaction is conceived for *E*-olefin **9a**, which produced **21a** as the major peroxide. However, prediction of a stable conformer(s) and the preferable course of the O_3 access to the *E*-olefin is presently difficult because the low $A^{1,3}$ strain of the *E*-olefin allows several low energy conformers of the C_{olefin}–$C_{allylic}$ σ bond and that the orbital interaction with $C_{allylic}$–C_{pentyl} or $C_{allylic}$–O_{TBDMS} would not be a decisive factor as suggested by the observed ratio of ca. 4:1 for **13a**.

The *vic*-diol structure is found in the metabolites of fatty acids, which have anti-inflammatory properties. Among them, 14*R*,15*S*-diHETE (**22**),[17,18] a derivative of arachidonic acid, was selected as the synthetic target. This target compound is not commercially available, and the three chemical syntheses so far published[19,17a] do not provide information about the stereoselectivity and/or yield. A similar biological potency was found in the *syn* diastereomer **23**,[17e] which was also chosen as a target. We envisaged the syntheses of these targets using aldehydes (2*S*,3*S*)-**10a** and (2*R*,3*S*)-**14a**, as shown in Schemes 4 and 5, respectively. Synthesis of these aldehydes in racemic forms has already been described in the abovementioned paragraphs. Furthermore, we intended to use the TMS group in the aldehydes as a protective group during further transformation.

Synthesis of 14*R*,15*S*-diHETE (**22**) depicted in Scheme 5 commenced with asymmetric hydrogenation of ketone **26** to afford propargylic alcohol (*S*)-**7a** (98.5% ee by chiral HPLC analysis), which was converted to (*S*)-**9a** by Red-Al reduction and subsequent silylation with TBDMSCl. Ozonolysis of the TBDMS ether afforded a mixture of (2*S*,3*S*)-**10a** (*anti* isomer) and the *syn* isomer (2*R*,3*S*)-**14a** in approximately 4:1 ratio. The conjugated olefin was formed in the aldehyde by the HWE-type olefination with phosphate **25** and the resulting ester were reduced with DIBAL in CH_2Cl_2, where most of the TMS group on the *syn* isomer was removed. Subsequently, Swern oxidation of **29** produced aldehyde **30** in 63% yield after separation of the remaining *syn* isomer by preparative HPLC. Wittig reaction of the aldehyde with the ylide derived



Scheme 3 Proposed reaction pathways.

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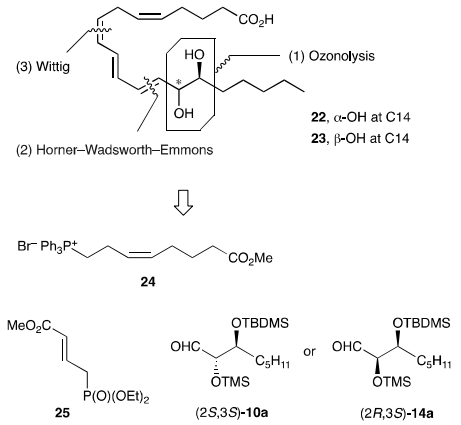


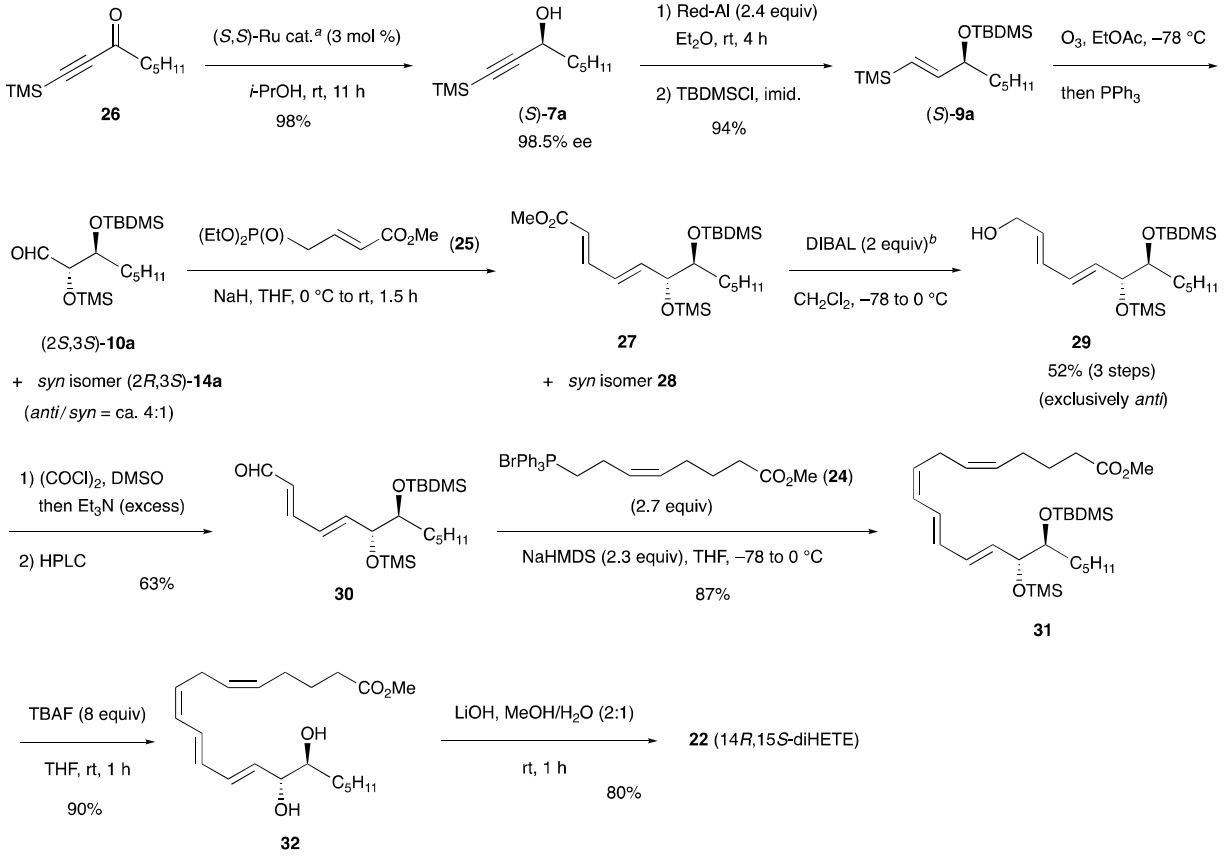
Scheme 4 Retrosynthesis of 14*R*,15*S*- and 14*S*,15*S*-diHETEs.

from phosphonium salt **24**[20,21] and NaHMDS stereoselectively furnished triene **31**, and the removal of the TBDMS groups afforded dihydroxy ester **32** in 90% yield. Finally, hydrolysis gave solid 14*R*,15*S*-diHETE (**22**) in good yield. The ^{1}H NMR spectrum of **32** (ester) was identical with the reported data.[17a] The ^{1}H and ^{13}C–APT NMR spectra, UV spectrum and HRMS data of **22** were consistent with the structure.

For the synthesis of 14*S*,15*S*-diHETE (**23**), propargylic alcohol (*S*)-**7a** (97.6% ee) prepared again was reduced to *Z*-olefin (*S*)-**12a**, which was silylated to (*S*)-**13a** with TBDMSCl (Scheme 6). The TBDMS ether was then subjected to ozonolysis to afford aldehyde (2*R*,3*S*)-**14a** as the major product over the *anti* isomer (ca. 5:1), and the mixture was converted to *syn* and *anti* esters **28** and **27**. To prevent desilylation of the TMS group from the less stable *syn* isomer, DIBAL reduction was carried out in Et_2O successfully, and the resulting alcohols were converted to aldehydes **34** and **30**. At this stage the isomers were separated by preparative HPLC to obtain *syn* isomer **34** in 39% yield. Further transformation of **34** to **23** proceeded uneventfully.

Conclusions

Ozonolysis of TBDMS, TES and TBDPS ethers of (*E*)- and (*Z*)-TMS-substituted secondary allylic alcohols **9a–e** and **13a–e** produced *anti* and *syn* isomers, respectively, after reductive



Scheme 5 Synthesis of 14*R*,15*S*-diHETE (**22**).

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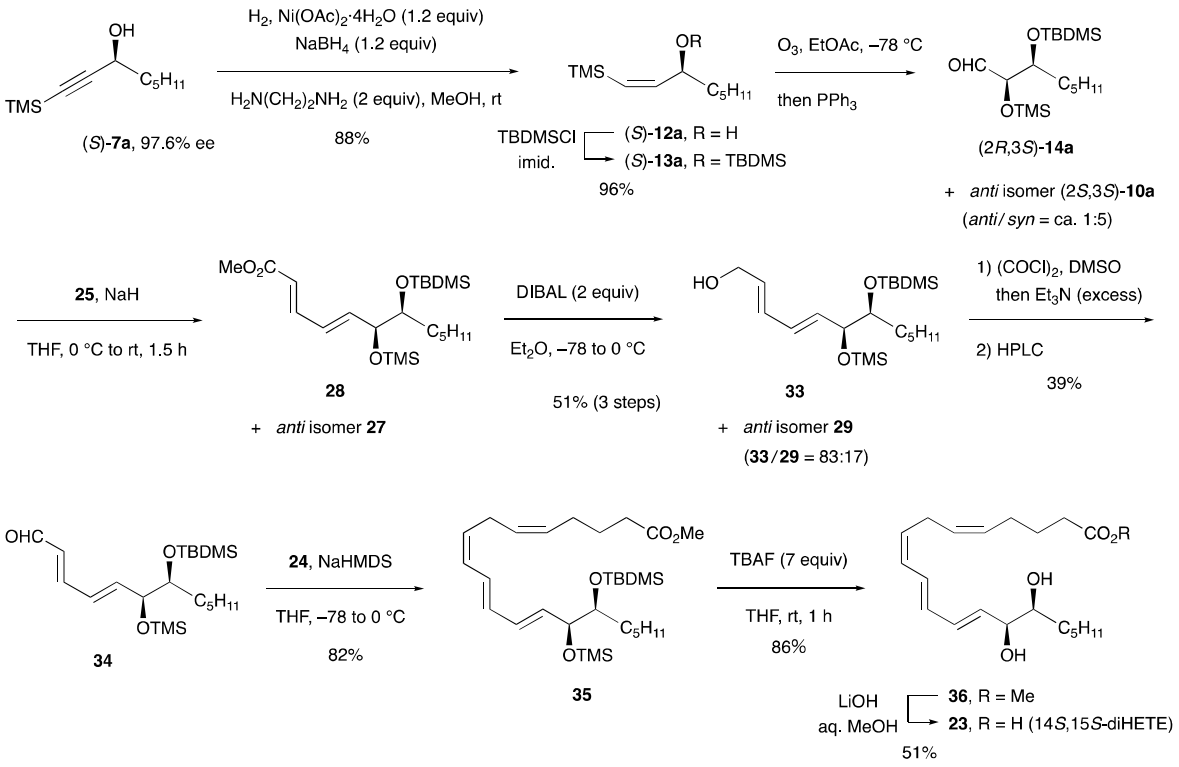
[a] (RuCl[(1*S*,2*S*)-TsDPEN](*p*-cymene). [b] TMS of the syn isomer was removed.



Scheme 6 Synthesis of 14*S*,15*S*-diHETE (**23**)

work-up with Ph_3P. The stereochemical outcome could be explained by the Cieplak effect. This reaction was applied successfully for synthesis of *anti* and *syn* isomers of 14,15-diHETE (**22** and **23**), potential inhibitors of LTB_4-induced inflammation.

Experimental

General methods. The ^1H (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectroscopic data were recorded in $CDCl_3$ using Me_4Si (δ = 0 ppm) and the centerline of the triplet (δ = 77.1 ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by minus (for C and CH_2) and plus (for CH and CH_3) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer with EI and FAB ionization modes. The solvents that were distilled prior to use were THF (from Na/benzophenone), Et_2O (from Na/benzophenone) and CH_2Cl_2 (from CaH_2). The reaction products were purified by chromatography on silica gel (Kanto, spherical silica gel 60N). Following reactions are described in the ESI: synthesis of **9b**, **9c**, **13b** and **13c**; ozonolysis and subsequent conversion to diols **11b**, **11c**, **15b** and **15c**; synthesis of **24** and **25**.

1-(Trimethylsilyl)oct-1-yn-3-ol (7a). To a solution of trimethylsilylacetylene (6.20 mL, 44.8 mmol, 1.5 equiv) in THF (60 mL) was added *n*-BuLi (22.0 mL, 1.6 M in hexane, 35.2 mmol, 1.2 equiv) at –78 °C. After 30 min of stirring at –78 °C, hexanal (2.99 g, 29.8 mmol, 1.0 equiv) in THF (40 mL) was added slowly. The solution was warmed to rt over 3 h before addition of saturated NH_4Cl solution (aq.). The mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give alcohol **7a** (5.91 g, 100%): colorless liquid; R_f 0.55 (hexane/EtOAc 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 0.90 (t, *J* = 6.9 Hz, 3 H), 1.24–1.74 (m, 8 H), 1.76 (d, *J* = 6.0 Hz, 1 H), 4.35 (dt, *J* = 6.0, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.1, 14.0, 22.5, 24.8, 31.4, 37.6, 62.7, 89.0, 107.2. The ^1H and ^{13}C NMR spectra were identical with those reported.[7b]

(*E*)-*tert*-Butyldimethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (9a). To an ice-cold solution of alcohol **7a** (1.41 g, 7.11 mmol, 1.0 equiv) in Et_2O (14 mL) was added Red-Al (4.00 mL, 3.6 M in toluene, 14.4 mmol, 2.0 equiv) dropwise. The solution was stirred at rt for 3 h and the reaction was quenched by addition of 1 N HCl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$, and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give allylic alcohol **8a** (1.33 g, 93%).

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A solution of allylic alcohol **8a** (708 mg, 3.53 mmol, 1.0 equiv), TBDMSCl (810 mg, 5.37 mmol, 1.5 equiv) and imidazole (484 mg, 7.11 mmol, 2.0 equiv) in DMF (7 mL) was stirred at rt for 2 h and diluted with saturated $NaHCO_3$ solution (aq.). The resulting mixture was extracted with hexane three times. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane) to give silyl ether **9a** (1.07 g, 96%): colorless liquid; R_f 0.87 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.05 (s, 9 H), 0.88 (t, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 1.18–1.51 (m, 8 H), 4.03 (q, J = 5.7 Hz, 1 H), 5.73 (d, J = 18.9 Hz, 1 H), 5.94 (dd, J = 18.9, 5.7 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.6 (+), –4.0 (+), –1.1 (+), 14.2 (+), 18.5 (–), 22.8 (–), 25.2 (–), 26.1 (+), 32.0 (–), 38.0 (–), 76.1 (+), 128.3 (+), 149.8 (+); HRMS (FAB$^+$) calcd for $C_{17}H_{38}OSi_2Na$ [(M+Na)$^+$] 337.2359, found 337.2369.

(*E*)-Triethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (9d). According to the procedure for the synthesis of **9a**, a solution of allylic alcohol **8a** (202 mg, 1.00 mmol, 1.0 equiv), TESCl (0.251 mL, 1.50 mmol, 1.5 equiv) and imidazole (140 mg, 2.06 mmol, 2.1 equiv) in DMF (2 mL) was stirred at rt for 2 h to afford silyl ether **9d** (271 mg, 86%): colorless liquid; R_f 0.85 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.58 (q, J = 7.8 Hz, 6 H), 0.88 (t, J = 6.6 Hz, 3 H), 0.94 (t, J = 7.8 Hz, 9 H), 1.19–1.52 (m, 8 H), 4.02 (q, J = 6.0 Hz, 1 H), 5.73 (d, J = 18.6 Hz, 1 H), 5.96 (dd, J = 18.6, 6.0 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –1.3 (+), 5.0 (–), 6.9 (+), 14.1 (+), 22.7 (–), 25.2 (–), 31.9 (–), 37.9 (–), 76.0 (+), 128.5 (+), 149.5 (+); HRMS (FAB$^+$) calcd for $C_{17}H_{37}OSi_2$ [(M–H)$^+$] 313.2383, found 313.2383.

(*E*)-*tert*-Butyldiphenyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (9e). According to the procedure for the synthesis of **9a**, a solution of allylic alcohol **8a** (305 mg, 1.52 mmol, 1.0 equiv), TBDPSCl (0.79 mL, 3.05 mmol, 2.0 equiv) and imidazole (262 mg, 3.85 mmol, 2.5 equiv) in DMF (3 mL) was stirred at rt for 4 h to afford silyl ether **9e** (571 mg, 86%): colorless liquid; R_f 0.80 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.04 (s, 9 H), 0.82 (t, J = 7.2 Hz, 3 H), 1.05 (s, 9 H), 1.10–1.53 (m, 8 H), 4.07 (q, J = 6.3 Hz, 1 H), 5.49 (d, J = 18.3 Hz, 1 H), 5.92 (dd, J = 6.3, 18.6 Hz, 1 H), 7.28–7.47 (m, 6 H), 7.73–7.58 (m, 4 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –1.3 (+), 14.1 (+), 19.5 (–), 22.6 (–), 24.5 (–), 27.2 (+), 31.8 (–), 37.6 (–), 76.9 (+), 127.4 (+), 127.5 (+), 129.3 (+), 129.4 (+), 129.6 (+), 134.6 (–), 136.1 (+), 136.2 (+), 148.7 (+); HRMS (FAB$^+$) calcd for $C_{27}H_{41}OSi_2$ [(M–H)$^+$] 437.2696, found 437.2702.

(*Z*)-*tert*-Butyldimethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (13a). To a mixture of $Ni(OAc)_2{\cdot}4H_2O$ (600 mg, 2.41 mmol, 1.2 equiv) in MeOH (3 mL) was added $NaBH_4$ (92 mg, 2.43 mmol, 1.2 equiv) portionwise. The flask was purged with hydrogen, and ethylenediamine (0.273 mL, 4.04 mmol, 2.0 equiv) was added. After 10 min, alcohol **7a** (392 mg, 1.98 mmol, 1.0 equiv) in MeOH (1 mL) was added. The mixture was stirred at rt for 6 h, diluted with hexane/EtOAc (1:1) and filtered through a pad of silica gel. The filtrate was washed with saturated NH_4Cl solution (aq.). The aqueous layer was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc 9:1) to afford allylic alcohol **12a** (321 mg, 81%).

A solution of allylic alcohol **12a** (147 mg, 0.734 mmol, 1.0 equiv), TBDMSCl (175 mg, 1.16 mmol, 1.6 equiv) and imidazole (100 mg, 1.47 mmol, 2.0 equiv) in DMF (2 mL) was stirred at rt for 2 h and diluted with saturated $NaHCO_3$ solution (aq.). The resulting mixture was extracted with hexane three times. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane) to give silyl ether **13a** (221 mg, 96%): colorless liquid; R_f 0.88 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.12 (s, 9 H), 0.87 (s, 9 H), 0.88 (t, J = 6.0 Hz, 3 H), 1.17–1.53 (m, 8 H), 4.22 (dt, J = 3.3, 8.4 Hz, 1 H), 5.42 (d, J = 14.7 Hz, 1 H), 6.21 (dd, J = 14.7, 8.4 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.3 (+), –3.8 (+), 0.5 (+), 14.2 (+), 18.3 (–), 22.8 (–), 25.3 (–), 26.0 (+), 32.0 (–), 39.0 (–), 73.3 (+), 127.1 (+), 152.8 (+); HRMS (FAB$^+$) calcd for $C_{17}H_{38}OSi_2Na$ [(M+Na)$^+$] 337.2359, found 337.2368.

(*Z*)-Triethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (13d). According to the procedure for the synthesis of **13a**, a solution of allylic alcohol **12a** (203 mg, 1.01 mmol, 1.0 equiv), TESCl (0.251 mL, 1.50 mmol, 1.5 equiv) and imidazole (137 mg, 2.01 mmol, 2.0 equiv) in DMF (2 mL) was stirred at rt for 2 h to afford silyl ether **13d** (274 mg, 87%): colorless liquid; R_f 0.83 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 0.58 (q, J = 8.1 Hz, 6 H), 0.88 (t, J = 6.9 Hz, 3 H), 0.94 (t, J = 8.1 Hz, 9 H), 1.19–1.54 (m, 8 H), 4.21 (dt, J = 3.9, 8.4 Hz, 1 H), 5.43 (d, J = 14.4 Hz, 1 H), 6.23 (dd, J = 14.4, 8.4 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 0.4 (+), 5.2 (–), 7.0 (+), 14.1 (+), 22.8 (–), 25.2 (–), 32.0 (–), 39.0 (–), 73.1 (+), 127.3 (+), 152.4 (+); HRMS (FAB$^+$) calcd for $C_{17}H_{38}OSi_2Na$ [(M+Na)$^+$] 337.2359, found 337.2369.

(*Z*)-*tert*-Butyldiphenyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane (13e). According to the procedure for the synthesis of **13a**, a solution of allylic alcohol **12a** (375 mg, 1.87 mmol, 1.0 equiv), TBDPSCl (0.97 mL, 3.74 mmol, 2.0 equiv) and imidazole (328 mg, 4.82 mmol, 2.6 equiv) in DMF (4 mL) was stirred at rt for 4 h to afford silyl ether **13e** (727 mg, 87%): colorless liquid; R_f 0.80 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.19 (s, 9 H), 0.83 (t, J = 7.5 Hz, 3 H), 1.04 (s, 9 H), 1.10–1.53 (m, 8 H), 4.25 (dt, J = 8.4, 5.7 Hz, 1 H), 5.35 (d, J = 14.7 Hz, 1 H), 6.31 (dd, J = 14.7, 8.4 Hz, 1 H), 7.29–7.45 (m, 6 H), 7.62–7.71 (m, 4 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 0.2 (+), 14.2 (+), 19.5 (–), 22.7 (–), 24.6 (–), 27.2 (+), 32.1 (–), 39.0 (–), 73.9 (+), 127.5 (+), 127.6 (+), 127.9 (+), 129.6 (+), 129.7 (+), 134.5 (–), 134.7 (–), 136.1 (+), 136.3 (+), 151.2 (+); HRMS (FAB$^+$) calcd for $C_{27}H_{41}OSi_2$ [(M–H)$^+$] 437.2696, found 437.2688.

Ethyl (4*R,5*S**,*E*)-4,5-dihydroxydec-2-enoate (11a) from TBDMS ether 9a.**

A solution of silyl ether **9a** (*E*/*Z* 94:6 by ^{1}H NMR, 299 mg, 0.950 mmol, 1.0 equiv) in EtOAc (13 mL) at −78 °C was gently bubbled with O_3 in O_2. After 15 min at −78 °C, nitrogen gas was introduced to the solution for 15 min to remove O_3, and

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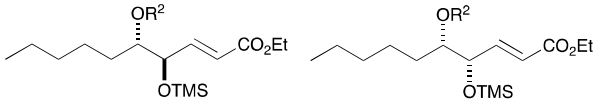
Ph_3P (1.20 g, 4.58 mmol, 5 equiv) was added. The mixture was warmed to rt, stirred at rt for 30 min and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc 9:1) to afford aldehyde **10a**.

To an ice-cold mixture of NaH (60 wt %, 51 mg, 1.28 mmol, 1.3 equiv) in THF (4 mL) was added a solution of $(EtO)_2P(O)CH_2CO_2Et$ (0.268 mL, 1.34 mmol, 1.4 equiv) dropwise. The mixture was stirred at 0 °C for 30 min. A solution of the above aldehyde in THF (2 mL) was added to the mixture. After 1 h of stirring at rt, the reaction was quenched by adding saturated NH_4Cl solution (aq.). The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give silyl ether **40a**.



40a, R^2 = TBDMS **41a**, R^2 = TBDMS
40d, R^2 = TES **41d**, R^2 = TES
40e, R^2 = TBDPS **41e**, R^2 = TBDPS

To a solution of the above silyl ether **40a** in THF (10 mL) was added TBAF (1.0 M in THF, 4.75 mL, 4.75 mmol, 5 equiv) dropwise. The solution was stirred at rt for 1 h and diluted with saturated $NaHCO_3$ solution (aq.). The mixture was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 1:1) to afford a mixture of *anti* diol **11a** and the *syn* isomer **15a** (*anti*/*syn* 81:19 by ^{1}H NMR, 145 mg, 66% over three steps): colorless liquid; R_f 0.55 (hexane/EtOAc 1:1). The *anti* isomer **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.23–1.58 (m, 8 H), 2.07 (br s, 1 H), 2.44 (br s, 1 H), 3.72–3.82 (m, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 4.28–4.36 (m, 1 H), 6.11 (dd, J = 15.6, 1.5 Hz, 1 H), 6.96 (dd, J = 15.6, 5.1 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 13.9 (+), 14.1 (+), 22.5 (–), 25.6 (–), 31.7 (–), 31.8 (–), 60.6 (–), 74.16 (+), 74.22 (+), 122.2 (+), 146.2 (+), 166.7 (–).

Ethyl (*E*)-3-[(4*R,5*S**)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl]acrylate (16) and ethyl (*E*)-3-[(4*S**,5*S**)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl]acrylate (17).** A solution of a mixture of diols **11a**/**15a** (47 mg, 0.204 mmol, 1.0 equiv), 2,2-dimethoxypropane (0.128 mL, 1.04 mmol, 5 equiv) and PPTS (5.4 mg, 0.022 mmol, 0.1 equiv) in DMF (2 mL) was stirred at rt–50 °C for 5 h and diluted with saturated $NaHCO_3$ solution (aq.). The mixture was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to afford *anti* acetonide **16** (32 mg, 58%) and *syn* acetonide **17** (10 mg, 18%). The *anti* isomer **16**: colorless liquid; R_f 0.42 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.36 (s, 3 H), 1.50 (s, 3 H), 1.21–1.58 (m, 8 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.17–4.27 (m, 1 H), 4.62 (dt, J = 1.5, 6.3 Hz, 1 H), 6.04 (dd, J = 15.6, 1.5 Hz, 1 H), 6.83 (dd, J = 15.6, 6.3 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.0 (+), 14.3 (+), 22.6 (–), 25.6 (+), 26.0 (–), 28.1 (+), 30.5 (–), 31.8 (–), 60.6 (–), 77.5 (+), 78.4 (+), 108.8 (–), 123.0 (+), 143.9 (+), 166.1 (–). The reported ^{1}H NMR spectrum[22] was updated. The *syn* isomer **17**: colorless liquid; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.43 (s, 3 H), 1.19–1.69 (m, 8 H), 3.73 (dt, J = 8.4, 6.0 Hz, 1 H), 4.14 (ddd, J = 8.4, 5.7, 1.5 Hz, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 6.11 (dd, J = 15.6, 1.5 Hz, 1 H), 6.86 (dd, J = 15.6, 5.7 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 14.3 (+), 22.6 (–), 25.7 (–), 26.7 (+), 27.4 (+), 31.9 (–), 32.1 (–), 60.7 (–), 80.3 (+), 80.7 (+), 109.4 (–), 122.8 (+), 144.3 (+), 166.1 (–). The ^{1}H NMR spectrum was identical with that reported.[12]

Ethyl (4*R,5*S**,*E*)-4,5-dihydroxydec-2-enoate (11a) from TES ether 9d.** According to the procedure for the synthesis of **11a** from **9a**, a solution of TES ether **9d** (*E*/*Z* 93:7 by ^{1}H NMR, 172 mg, 0.547 mmol, 1.0 equiv) in EtOAc (8 mL) at −78 °C was gently bubbled with O_3 in O_2 and then the product was treated with Ph_3P (706 mg, 2.69 mmol, 5 equiv) to afford aldehyde **10d**, which was dissolved in THF (1 mL) and added to a mixture of NaH (60 wt %, 29 mg, 0.725 mmol, 1.3 equiv) and $(EtO)_2P(O)CH_2CO_2Et$ (0.155 mL, 0.774 mmol, 1.4 equiv) in THF (2 mL). The mixture was stirred at rt for 2 h to give silyl ether **40d**. A solution of **40d** and TBAF (1.0 M in THF, 2.70 mL, 2.70 mmol, 5 equiv) in THF (5 mL) was stirred at rt for 2 h to produce a mixture of *anti* diol **11a** and the *syn* isomer **15a** (*anti*/*syn* 75:25 by ^{1}H NMR, 86 mg, 69% over three steps).

Ethyl (4*R,5*S**,*E*)-4,5-dihydroxydec-2-enoate (11a) from TBDPS ether 9e.** According to the procedure for the synthesis of **11a** from **9a**, a solution of silyl ether **9e** (*E*/*Z* 95:5 by ^{1}H NMR, 253 mg, 0.577 mmol, 1.0 equiv) in EtOAc (8 mL) at −78 °C was gently bubbled with O_3 in O_2 and then the product was treated with Ph_3P (752 mg, 2.87 mmol, 5 equiv) to afford aldehyde **10e**, which was dissolved in THF (1 mL) and added to a mixture of NaH (60 wt %, 29 mg, 0.725 mmol, 1.3 equiv) and $(EtO)_2P(O)CH_2CO_2Et$ (0.165 mL, 0.824 mmol, 1.4 equiv) in THF (2 mL). The mixture was stirred at rt for 2 h to afford silyl ether **40e**. A solution of **40e** and TBAF (1.0 M in THF, 2.90 mL, 2.90 mmol, 5 equiv) in THF (6 mL) was stirred at rt for 3 h to afford a mixture of *anti* diol **11a** and the *syn* isomer **15a** (*anti*/*syn* 73:27 by ^{1}H NMR, 73 mg, 55% over three steps).

Ethyl (4*S,5*S**,*E*)-4,5-dihydroxydec-2-enoate (15a) from TBDMS ether 13a.** According to the procedure for the synthesis of **11a** from **9a**, a solution of silyl ether **13a** (*Z*/*E* 96:4 by ^{1}H NMR, 301 mg, 0.957 mmol, 1.0 equiv) in EtOAc (13 mL) at −78 °C was gently bubbled with O_3 in O_2 and the product was treated with PPh_3 (1.20 g, 4.58 mmol, 5 equiv) to produce aldehyde **14a**, which was dissolved in THF (2 mL) and added to a mixture of NaH (60 wt %, 51 mg, 1.28 mmol, 1.3 equiv) and $(EtO)_2P(O)CH_2CO_2Et$ (0.270 mL, 1.35 mmol, 1.4 equiv) in THF (4 mL). The mixture was stirred at rt for 1 h to afford silyl ether **41a**. A solution of **41a** and TBAF (1.0 M in THF, 4.80 mL, 4.80 mmol, 5 equiv) in THF (10 mL) was stirred at rt for 1 h to give a mixture of *syn* diol **15a** and the *anti* isomer **11a** (*syn*/*anti* 84:16 by ^{1}H NMR, 108 mg, 49% over three steps): colorless liquid; R_f 0.55 (hexane/EtOAc 1:1). The

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syn isomer **15a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.2 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.18–1.53 (m, 8 H), 3.34 (br s, 2 H), 3.44–3.55 (m, 1 H), 4.07 (t, J = 5.4 Hz, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 6.08 (d, J = 15.6 Hz, 1 H), 6.90 (dd, J = 15.6, 5.4 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.0 (+), 14.1 (+), 22.6 (–), 25.3 (–), 31.7 (–), 33.0 (–), 60.7 (–), 74.1 (+), 74.2 (+), 122.1 (+), 147.4 (+), 166.7 (–). The ^{1}H NMR spectrum was identical with that reported.[12]

Ethyl (4*S,5*S**,*E*)-4,5-dihydroxydec-2-enoate (15a) from TES ether 13d.** According to the procedure for the synthesis of **11a** from **9a**, a solution of silyl ether **13d** (*Z*/*E* 95:5 by ^{1}H NMR, 170 mg, 0.540 mmol, 1.0 equiv) in EtOAc (8 mL) at −78 °C was gently bubbled with O_3 in O_2 and the product was treated with PPh_3 (705 mg, 2.69 mmol, 5 equiv) to afford aldehyde **14d**, which was dissolved in THF (1 mL) and added to a mixture of NaH (60 wt %, 27 mg, 0.675 mmol, 1.3 equiv) and $(EtO)_2P(O)CH_2CO_2Et$ (0.155 mL, 0.774 mmol, 1.4 equiv) in THF (2 mL). The mixture was stirred at rt for 1 h to afford silyl ether **41d**. A solution of **41d** and TBAF (1.0 M in THF, 2.70 mL, 2.70 mmol, 5 equiv) in THF (5 mL) was stirred at rt for 2 h to afford a mixture of *syn* diol **15a** and the *anti* isomer **11a** (*syn*/*anti* 79:21 by ^{1}H NMR, 67 mg, 54% over three steps).

Ethyl (4*S,5*S**,*E*)-4,5-dihydroxydec-2-enoate (15a) from TBDPS ether 13e.** According to the procedure for the synthesis of **11a** from **9a**, a solution of silyl ether **13e** (*Z*/*E* 95:5 by ^{1}H NMR, 194 mg, 0.442 mmol, 1.0 equiv) in EtOAc (6 mL) at −78 °C was gently bubbled with O_3 in O_2 and the product was treated with PPh_3 (572 mg, 2.18 mmol, 5 equiv) to afford aldehyde **14e**, which was dissolved in THF (1 mL) and added to a mixture of NaH (60 wt %, 22 mg, 0.55 mmol, 1.2 equiv) and $(EtO)_2P(O)CH_2CO_2Et$ (0.125 mL, 0.624 mmol, 1.4 equiv) in THF (2 mL). The mixture was stirred at rt for 2 h to produce silyl ether **41e**. A solution of **41e** and TBAF (1.0 M in THF, 2.20 mL, 2.20 mmol, 5 equiv) in THF (4 mL) was stirred at rt for 3 h to afford a mixture of diol **15a** and the *anti* isomer **11a** (*syn*/*anti* 88:12 by ^{1}H NMR, 45 mg, 44% over three steps).

(*S*)-1-(Trimethylsilyl)oct-1-yn-3-ol [(*S*)-7a]. A mixture of racemic alcohol **7a** (5.01 g, 25.3 mmol, 1.0 equiv), PCC (8.27 g, 38.4 mmol, 1.5 equiv) and Celite (12 g) in CH_2Cl_2 (130 mL) was stirred vigorously at rt for 8 h and diluted with hexane. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc 19:1) to afford ketone **26** (3.96 g, 80%).

RuCl[(1*S*,2*S*)-TsDPEN](*p*-cymene) (296 mg, 0.466 mmol, 3 mol%) was neutralized with KOH (ca. 800 mg, 14 mmol) in CH_2Cl_2 (15 mL), and the mixture was washed with H_2O, dried over CaH_2 and concentrated under vacuum to afford a residue, which was diluted with *i*-PrOH (19 mL) and transferred to a solution of ketone **26** (3.10 g, 15.8 mmol, 1.0 equiv) in *i*-PrOH (57 mL). The solution was stirred at rt for 11 h and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give alcohol (*S*)-**7a** (3.08 g, 98%), which was 98.5% ee as determined by chiral HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 99/1, 1.0 mL/min, 35 °C, t_R/min = 9.21 (*S*-isomer, major), 9.68 (*R*-isomer, minor)): colorless liquid; $[\alpha]_D^{21}$ –1.6 (*c* 1.26, $CHCl_3$); *cf.* lit.[7a] $[\alpha]_D^{23}$ –2.5 (*c* 10.15, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were identical with those of racemic alcohol **7a**.

(*S,E*)-*tert*-Butyldimethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane [(*S*)-9a]. The procedure for the conversion of racemic **7a** to **9a** was repeated with (*S*)-**7a** (2.81 g, 14.2 mmol, 1.0 equiv) and Red-Al (3.6 M in toluene, 9.4 mL, 33.9 mmol, 2.4 equiv) in Et_2O (28 mL) at rt for 4 h to give (*S*)-**8a** (2.85 g, 94%). A solution of the alcohol (2.69 g, 13.4 mmol, 1.0 equiv), TBDMSCl (2.48 g, 16.5 mmol, 1.2 equiv) and imidazole (1.39 g, 20.4 mmol, 1.5 equiv) in DMF (27 mL) was stirred at rt for 2 h to afford silyl ether (*S*)-**9a** (4.50 g, quant.): colorless liquid; $[\alpha]_D^{20}$ –16 (*c* 1.54, $CHCl_3$).

(2*E*,4*E*,6*R*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6-[(trimethylsilyl)oxy]dodeca-2,4-dien-1-ol (29). According to the procedure for the ozonolysis of racemic **9a**, a solution of (*S*)-**9a** (1.01 g, 3.21 mmol, 1.0 equiv) in EtOAc (40 mL) at −78 °C was gently bubbled with O_3 in O_2 and the product was treated with PPh_3 (1.65 g, 6.29 mmol, 2.0 equiv) to afford aldehyde (2*S*,3*S*)-**10a** as the major isomer.

To an ice-cold mixture of NaH (60 wt %, 154 mg, 3.85 mmol, 1.2 equiv) in THF (6 mL) was added a solution of phosphonate **25** (1.14 g, 4.83 mmol, 1.5 equiv) in THF (6 mL) dropwise. After 30 min of stirring at 0 °C, a solution of the above aldehyde in THF (6 mL) was added. The mixture was stirred at rt for 1 h and diluted with saturated NH_4Cl solution (aq.). The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane to hexane/EtOAc 19:1) to afford ester **27** as the major isomer.

To a solution of the above ester in CH_2Cl_2 (16 mL) was added DIBAL (1.0 M in hexane, 6.20 mL, 6.20 mmol, 1.9 equiv) at –78 °C. After 30 min at 0 °C, the mixture was poured into H_2O (1.14 mL, 63.4 mmol, 20 equiv), NaF (1.33 g, 31.7 mmol, 10 equiv) and Celite (1.30 g) with vigorous stirring. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give alcohol **29** (665 mg, 52% in three steps): colorless liquid; R_f 0.45 (hexane/EtOAc 4:1); $[\alpha]_D^{20}$ –12.6 (*c* 1.005, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.09 (s, 9 H), 0.87 (s, 9 H), 0.88 (t, J = 7.2 Hz, 3 H), 1.18–1.48 (m, 9 H), 3.54–3.60 (m, 1 H), 3.94 (dd, J = 7.2, 5.2 Hz, 1 H), 4.19 (t, J = 5.4 Hz, 2 H), 5.72 (dd, J = 15.2, 7.2 Hz, 1 H), 5.80 (dt, J = 14.8, 5.4 Hz, 1 H), 6.11 (dd, J = 15.2, 10.8 Hz, 1 H), 6.25 (dd, J = 14.8, 10.8 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ –4.5 (+), –3.9 (+), 0.5 (+), 14.1 (+), 18.3 (–), 22.7 (–), 24.8 (–), 26.1 (+), 32.2 (–), 33.8 (–), 63.5 (–), 76.4 (+), 76.6 (+), 130.5 (+), 131.3 (+), 131.5 (+), 134.8 (+); HRMS (FAB^+) calcd for $C_{21}H_{44}O_3Si_2Na$ [$(M+Na)^+$] 423.2727, found 423.2728.

Note that during the above DIBAL reduction of the *anti* (major) and *syn* isomers in CH_2Cl_2, the TMS group in the *syn* isomer was removed. Cf. the DIBAL reduction of the *syn* isomer was carried out in Et_2O (vide infra).

(2*E*,4*E*,6*R*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6-[(trimethylsilyl)oxy]dodeca-2,4-dienal (30). To a solution of

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$(COCl)_2$ (0.195 mL, 2.27 mmol, 3 equiv) in CH_2Cl_2 (6 mL) was slowly added DMSO (2.0 M in CH_2Cl_2, 2.24 mL, 4.48 mmol, 6 equiv) at −78 °C. A solution of alcohol **29** (293 mg, 0.731 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added to the solution at −78 °C. After an additional 15 min of stirring at −78 °C, Et_3N (1.10 mL, 7.89 mmol, 11 equiv) was added. After being stirred at 0 °C for 15 min, the mixture was diluted with saturated $NaHCO_3$ solution (aq.) and extracted with hexane three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 19:1) to afford aldehyde **30** (271 mg, 93%), which was further purified by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 95:5, 20 mL/min). Aldehyde **30** (183 mg, 63%); colorless liquid; R_f 0.55 (hexane/EtOAc 9:1); $[\alpha]_D^{20}$ +0.93 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.11 (s, 9 H), 0.87 (s, 9 H), 0.89 (t, *J* = 6.8 Hz, 3 H), 1.18–1.53 (m, 8 H), 3.61 (dt, *J* = 6.0, 4.6 Hz, 1 H), 4.08 (t, *J* = 6.0 Hz, 1 H), 6.14 (dd, *J* = 15.2, 8.0 Hz, 1 H), 6.31 (dd, *J* = 15.4, 6.0 Hz, 1 H), 6.41 (dd, *J* = 15.4, 10.8 Hz, 1 H), 7.11 (dd, *J* = 15.2, 10.8 Hz, 1 H), 9.57 (d, *J* = 8.0, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ –4.6 (+), –4.1 (+), 0.2 (+), 14.0 (+), 18.2 (–), 22.6 (–), 24.6 (–), 25.9 (+), 32.0 (–), 33.8 (–), 75.8 (+), 76.2 (+), 128.6 (+), 131.4 (+), 146.0 (+), 151.7 (+), 193.9 (+); HRMS (FAB^+) calcd for $C_{21}H_{42}O_3Si_2Na$ [$(M+Na)^+$] 421.2570, found 421.2571.

Methyl (5*Z*,8*Z*,10*E*,12*E*,14*R*,15*S*)-15-[(*tert*-butyldimethylsilyl)oxy]-14-[(trimethylsilyl)oxy]icosa-5,8,10,12-tetraenoate (31). To an ice-cold solution of phosphonium salt **24** (561 mg, 1.13 mmol, 2.7 equiv) in THF (2 mL) was added NaHMDS (1.0 M in THF, 1.00 mL, 1.00 mmol, 2.3 equiv) dropwise. The mixture was stirred at 0 °C for 1 h and cooled to –78 °C. A solution of aldehyde **30** (170 mg, 0.426 mmol, 1.0 equiv) in THF (2 mL) was added to the mixture, which was then warmed to rt over 1 h and diluted with saturated NH_4Cl solution (aq.). The resulting mixture was extracted with hexane three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 19:1) to afford olefin **31** (200 mg, 87%): colorless liquid; R_f 0.65 (hexane/EtOAc 9:1); $[\alpha]_D^{20}$ –13 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.09 (s, 9 H), 0.87 (s, 9 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 1.18–1.49 (m, 8 H), 1.71 (quint., *J* = 7.2 Hz, 2 H), 2.12 (q, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 2.93 (t, *J* = 6.4 Hz, 2 H), 3.54–3.60 (m, 1 H), 3.67 (s, 3 H), 3.96 (dd, *J* = 7.2, 4.4 Hz, 1 H), 5.33–5.46 (m, 3 H), 5.67–5.77 (m, 1 H), 6.03 (t, *J* = 11.2 Hz, 1 H), 6.13–6.26 (m, 2 H), 6.40–6.51 (m, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.5 (+), –3.9 (+), 0.5 (+), 14.2 (+), 18.4 (–), 22.7 (–), 24.8 (–), 24.9 (–), 26.1 (+), 26.2 (–), 26.7 (–), 32.2 (–), 33.5 (–), 33.8 (–), 51.6 (+), 76.5 (+), 76.8 (+), 127.4 (+), 128.6 (+), 128.9 (+), 129.4 (+), 130.2 (+), 131.6 (+), 132.9 (+), 134.7 (+), 174.2 (–); HRMS (FAB^+) calcd for $C_{30}H_{55}O_4Si_2$ [$(M–H)^+$] 535.3639, found 535.3616.

Methyl (5*Z*,8*Z*,10*E*,12*E*,14*R*,15*S*)-14,15-dihydroxyicosa-5,8,10,12-tetraenoate (32). To an ice-cold solution of ether **31** (121 mg, 0.225 mmol, 1.0 equiv) in THF (1 mL) was added TBAF (1.0 M in THF, 1.79 mL, 1.79 mmol, 8 equiv) dropwise. The solution was stirred at rt for 1 h and diluted with McIlvaine's phosphate buffer (pH 5.0). The mixture was extracted with Et_2O three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 2:1) to afford diol **32** (71 mg, 90%), which was further purified by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 1:1, 20 mL/min): white solids; mp 42–43 °C; R_f 0.30 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ +9.4 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.20–1.55 (m, 8 H), 1.71 (quint., *J* = 7.6 Hz, 2 H), 1.99 (br s, 1 H), 2.11 (br s, 1 H), 2.12 (q, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.6 Hz, 2 H), 2.93 (t, *J* = 6.0 Hz, 2 H), 3.67 (s, 3 H), 3.63–3.76 (m, 1 H), 4.10–4.18 (m, 1 H), 5.34–5.48 (m, 3 H), 5.77 (dd, *J* = 15.2, 7.2 Hz, 1 H), 6.03 (t, *J* = 11.2 Hz, 1 H), 6.22 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.37 (dd, *J* = 15.2, 10.8 Hz, 1 H), 6.53 (dd, *J* = 14.8, 11.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.7 (–), 24.8 (–), 25.6 (+), 26.3 (–), 26.7 (–), 31.9 (–), 32.3 (–), 33.5 (–), 51.6 (+), 74.4 (+), 75.7 (+), 128.3 (+), 128.6 (+), 128.8 (+), 129.4 (+), 130.8 (+), 131.1 (+), 132.0 (+), 133.5 (+), 174.2 (–); HRMS (FAB^+) calcd for $C_{21}H_{34}O_4Na$ [$(M+Na)^+$] 373.2355, found 373.2363. The ^{1}H NMR spectrum was consistent with that reported.[17a]

(5*Z*,8*Z*,10*E*,12*E*,14*R*,15*S*)-14,15-Dihydroxyicosa-5,8,10,12-tetraenoic acid (14*R*,15*S*-diHETE) (22). To a solution of diol **32** (9.3 mg, 0.0265 mmol, 1.0 equiv) in MeOH (0.2 mL) and H_2O (0.1 mL) was added $LiOH·H_2O$ (10.4 mg, 0.248 mmol, 9 equiv). After 1 h of stirring at rt, McIlvaine's phosphate buffer (pH 5.0) was added. The resulting mixture was extracted with Et_2O three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 1:2) to afford 14*R*,15*S*-diHETE (**22**) (7.1 mg, 80%): white solids; mp 58–59 °C; R_f 0.35 (hexane/EtOAc 1:2); $[\alpha]_D^{20}$ +26 (*c* 0.71, $CHCl_3$); UV (MeOH) λ_{max} 263, 273, 284 nm (ε 40000, 53000, 42000); ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (t, *J* = 6.8 Hz, 3 H), 1.22–1.60 (m, 8 H), 1.66 (quint., *J* = 7.2 Hz, 2 H), 2.14 (q, *J* = 7.2 Hz, 2 H), 2.30 (t, *J* = 7.2 Hz, 2 H), 2.96 (t, *J* = 6.0 Hz, 2 H), 3.44–3.52 (m, 1 H), 3.96 (t, *J* = 6.6 Hz, 1 H), 4.64 (br s, 3 H), 5.32–5.47 (m, 3 H), 5.79 (dd, *J* = 14.8, 6.6 Hz, 1 H), 6.02 (t, *J* = 11.2 Hz, 1 H), 6.24 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.36 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.57 (dd, *J* = 14.8, 11.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, CD_3OD) δ 11.4 (+), 20.7 (–), 23.0 (–), 23.7 (+), 24.1 (–), 24.5 (–), 30.1 (–), 30.8 (–), 31.3 (–), 72.7 (+), 73.9 (+), 126.0 (+), 126.4 (+), 126.8 (+), 127.4 (+), 128.2 (+), 130.5 (+), 130.8 (+), 131.1 (+), 174.5 (–); HRMS (FAB^+) calcd for $C_{20}H_{31}O_4$ [$(M–H)^+$] 335.2222, found 335.2220.

(*S*,*Z*)-*tert*-Butyldimethyl[(1-(trimethylsilyl)oct-1-en-3-yl)oxy]silane [(*S*)-13a]. The conversion of racemic **7a** to **13a** was repeated with (*S*)-**7a**. In brief, alcohol (*S*)-**7a** (1.01 g, 5.09 mmol, 1.0 equiv) in MeOH (3 mL) was added to a mixture of $Ni(OAc)_2·4H_2O$ (1.51 g, 6.07 mmol, 1.2 equiv), $NaBH_4$ (223 mg, 5.89 mmol, 1.2 equiv) and ethylenediamine (0.680 mL, 10.1 mmol, 2.0 equiv) in MeOH (8 mL) under hydrogen, the mixture was stirred at rt for 5 h to afford allylic alcohol (*S*)-**12a** (890 mg, 88%). A solution of (*S*)-**12a** (1.04 g, 5.19 mmol, 1.0 equiv), TBDMSCl (913 mg, 6.06 mmol, 1.2 equiv) and

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imidazole (512 mg, 7.52 mmol, 1.4 equiv) in DMF (10 mL) was stirred at rt for 2 h to give silyl ether (*S*)-**13a** (1.57 g, 96%): colorless liquid; $[\alpha]_D^{21}$ –17 (*c* 1.28, $CHCl_3$).

(2*E*,4*E*,6*S*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6-[(trimethylsilyl)oxy]dodeca-2,4-dien-1-ol (33). According to the conversion of (*S*)-**9a** to ester **27**, a solution of (*S*)-**13a** (1.00 g, 3.18 mmol, 1.0 equiv) in EtOAc (40 mL) at −78 °C was gently bubbled with O_3 in O_2 and the product was treated with PPh_3 (1.64 g, 6.25 mmol, 2.0 equiv) to afford aldehyde (2*R*,3*S*)-**14a** as the major isomer, which was dissolved in THF (6 mL) and added to a mixture of NaH (60 wt %, 157 mg, 3.93 mmol, 1.2 equiv) and phosphonate **25** (1.13 g, 4.78 mmol, 1.5 equiv) in THF (12 mL) to give ester **28** as the major product.

To a solution of the above ester in Et_2O (16 mL) was added DIBAL (1.0 M in hexane, 6.20 mL, 6.20 mmol, 1.9 equiv) at −78 °C. After 15 min of stirring at −78 °C, the mixture was poured into H_2O (1.14 mL, 63.4 mmol, 20 equiv), NaF (1.33 g, 31.7 mmol, 10 equiv) and Celite (1.3 g) with vigorous stirring. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give a mixture of alcohol **33** and the *anti* isomer **29** (83:17 by ^{1}H NMR, 655 mg, 51% in three steps): colorless liquid; R_f 0.45 (hexane/EtOAc 4:1). The *syn* isomer **33**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.10 (s, 9 H), 0.87 (t, *J* = 7.6 Hz, 3 H), 0.89 (s, 9 H), 1.14–1.54 (m, 9 H), 3.50–3.59 (m, 1 H), 4.13 (t, *J* = 5.2 Hz, 1 H), 4.19 (t, *J* = 5.2 Hz, 2 H), 5.76–5.85 (m, 2 H), 6.20 (dd, *J* = 14.8, 10.4 Hz, 1 H), 6.28 (dd, *J* = 14.8, 10.4 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.6 (+), –4.1 (+), 0.3 (+), 14.1 (+), 18.1 (–), 22.7 (–), 25.5 (–), 25.9 (+), 31.5 (–), 32.0 (–), 63.3 (–), 75.4 (+), 75.8 (+), 129.7 (+), 131.1 (+), 131.3 (+), 133.5 (+).

(2*E*,4*E*,6*S*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6-[(trimethylsilyl)oxy]dodeca-2,4-dienal (34). To a solution of $(COCl)_2$ (0.195 mL, 2.27 mmol, 3 equiv) in CH_2Cl_2 (6 mL) was slowly added DMSO (2.0 M in CH_2Cl_2, 2.24 mL, 4.48 mmol, 6 equiv) at −78 °C. A solution of alcohol **33** and the *anti* isomer (301 mg, 0.751 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added to the solution at −78 °C. After an additional 15 min of stirring at −78 °C, Et_3N (1.10 mL, 7.89 mmol, 11 equiv) was added. After being stirred at 0 °C for 15 min, the mixture was diluted with saturated $NaHCO_3$ solution (aq.) and extracted with hexane three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 19:1) to afford aldehyde **34** and the *anti* isomer **30** (272 mg, 91%), which were separated by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 95:5, 20 mL/min). Aldehyde **34**: 117 mg (39%); colorless liquid; R_f 0.56 (hexane/EtOAc 9:1); $[\alpha]_D^{20}$ –123 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.13 (s, 9 H), 0.87 (t, *J* = 7.2 Hz, 3 H), 0.91 (s, 9 H), 1.08–1.56 (m, 8 H), 3.57–3.64 (m, 1 H), 4.27 (t, *J* = 3.6 Hz, 1 H), 6.14 (dd, *J* =15.2, 8.0 Hz, 1 H), 6.42 (dd, *J* = 15.2, 3.6 Hz, 1 H), 6.51 (dd, *J* = 15.2, 10.8 Hz, 1 H), 7.16 (dd, *J* = 15.2, 10.8 Hz, 1 H), 9.56 (d, *J* = 8.0, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.6 (+), –4.2 (+), 0.1 (+), 14.1 (+), 18.1 (–), 22.6 (–), 25.8 (–), 25.9 (+), 31.3 (–), 31.9 (–), 74.9 (+), 75.5 (+), 127.9 (+), 131.0 (+), 145.3 (+), 152.1 (+), 194.1 (+).

Methyl (5*Z*,8*Z*,10*E*,12*E*,14*S*,15*S*)-15-[(*tert*-butyldimethylsilyl)oxy]-14-[(trimethylsilyl)oxy]icosa-5,8,10,12-tetraenoate (35). To an ice-cold solution of phosphonium salt **24** (362 mg, 0.728 mmol, 2.6 equiv) in THF (1.4 mL) was added NaHMDS (1.0 M in THF, 0.68 mL, 0.68 mmol, 2.4 equiv) dropwise. The mixture was stirred at 0 °C for 1 h and cooled to –78 °C. A solution of aldehyde **34** (112 mg, 0.281 mmol, 1.0 equiv) in THF (1.4 mL) was added. The mixture was then warmed to 0 °C over 1 h and diluted with saturated NH_4Cl solution (aq.). The resulting mixture was extracted with hexane three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 19:1) to afford olefin **35** (124 mg, 82%): colorless liquid; R_f 0.65 (hexane/EtOAc 9:1); $[\alpha]_D^{23}$ –69 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 9 H), 0.87 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 1.14–1.54 (m, 8 H), 1.71 (quint., *J* = 7.2 Hz, 2 H), 2.12 (q, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 2.93 (t, *J* = 6.8 Hz, 2 H), 3.50–3.59 (m, 1 H), 3.67 (s, 3 H), 4.15 (t, *J* = 5.2 Hz, 1 H), 5.31–5.46 (m, 3 H), 5.75–5.84 (m, 1 H), 6.03 (t, *J* = 10.4 Hz, 1 H), 6.19–6.31 (m, 2 H), 6.40–6.51 (m, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.6 (+), –4.0 (+), 0.3 (+), 14.1 (+), 18.2 (–), 22.7 (–), 24.8 (–), 25.6 (–), 26.0 (+), 26.2 (–), 26.6 (–), 31.5 (–), 32.0 (–), 33.4 (–), 51.5 (+), 75.5 (+), 75.9 (+), 127.0 (+), 128.6 (+), 128.9 (+), 129.3 (+), 129.7 (+), 130.6 (+), 133.0 (+), 133.5 (+), 174.1 (–); HRMS (FAB^+) calcd for $C_{30}H_{56}O_4Si_2Na$ $[(M+Na)^+]$ 559.3615, found 559.3593.

Methyl (5*Z*,8*Z*,10*E*,12*E*,14*R*,15*S*)-14,15-dihydroxyicosa-5,8,10,12-tetraenoate (36). To an ice-cold solution of ester **35** (73 mg, 0.136 mmol, 1.0 equiv) in THF (0.7 mL) was added TBAF (1.0 M in THF, 1.00 mL, 1.00 mmol, 7 equiv) dropwise. The solution was stirred at rt for 1 h and diluted with McIlvaine's phosphate buffer (pH 5.0). The mixture was extracted with Et_2O three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 2:1) to afford diol **36** (41 mg, 86%), which was further purified by using recycling HPLC (LC-Forte/R equipped with YMC-Pack SIL-60, hexane/EtOAc 1:1, 20 mL/min): colorless liquid; R_f 0.30 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ –18 (*c* 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20–1.56 (m, 8 H), 1.71 (quint., *J* = 7.6 Hz, 2 H), 2.12 (q, *J* = 7.2 Hz, 2 H), 2.20–2.28 (m, 2 H), 2.33 (t, *J* = 7.6 Hz, 2 H), 2.93 (t, *J* = 6.6 Hz, 2 H), 3.44–3.52 (m, 1 H), 3.67 (s, 3 H), 3.93–4.01 (m, 1 H), 5.34–5.50 (m, 3 H), 5.69 (dd, *J* = 14.8, 7.0 Hz, 1 H), 6.03 (t, *J* = 10.8 Hz, 1 H), 6.21 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.39 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.54 (dd, *J* = 14.8, 10.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.7 (–), 24.8 (–), 25.4 (+), 26.3 (–), 26.7 (–), 31.9 (–), 33.0 (–), 33.6 (–), 51.6 (+), 74.8 (+), 76.0 (+), 128.3 (+), 128.5 (+), 128.9 (+), 129.5 (+), 131.2 (+), 131.9 (+), 132.3 (+), 133.2 (+), 174.2 (–); HRMS (FAB^+) calcd for $C_{21}H_{34}O_4Na$ $[(M+Na)^+]$ 373.2355, found 373.2356.

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(5*Z*,8*Z*,10*E*,12*E*,14*S*,15*S*)-14,15-Dihydroxyicosa-5,8,10,12-tetraenoic acid (14*S*,15*S*-diHETE) (23). To a solution of diol **36** (6.6 mg, 0.0188 mmol, 1.0 equiv) in MeOH (0.2 mL) and H_2O (0.1 mL) was added $LiOH{\cdot}H_2O$ (8.5 mg, 0.203 mmol, 11 equiv). After 1 h of stirring at rt, McIlvaine's phosphate buffer (pH 5.0) was added, and the resulting mixture was extracted with Et_2O three times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc 1:2) to afford 14*S*,15*S*-diHETE (**23**) (3.2 mg, 51%): colorless liquid; R_f 0.35 (hexane/EtOAc 1:2); $[\alpha]_D^{22}$ –21 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (t, *J* = 6.8 Hz, 3 H), 1.21–1.57 (m, 8 H), 1.66 (quint., *J* = 7.6 Hz, 2 H), 2.14 (q, *J* = 7.2 Hz, 2 H), 2.30 (t, *J* = 7.6 Hz, 2 H), 2.96 (t, *J* = 6.0 Hz, 2 H), 3.38–3.47 (m, 1 H), 3.94 (t, *J* = 7.2 Hz, 1 H), 4.87 (br s, 3 H) 5.31–5.49 (m, 3 H), 5.73 (dd, *J* = 15.2, 7.2 Hz, 1 H), 6.02 (t, *J* = 11.2 Hz, 1 H), 6.23 (dd, *J* = 14.8, 10.8 Hz, 1 H), 6.37 (dd, *J* = 15.2, 10.8 Hz, 1 H), 6.57 (dd, *J* = 14.8, 11.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, CD_3OD) δ 11.4 (+), 20.7 (–), 23.0 (–), 23.7 (+), 24.1 (–), 24.5 (–), 30.1 (–), 30.7 (–), 31.3 (–), 72.8 (+), 73.9 (+), 126.2 (+), 126.4 (+), 126.8 (+), 127.4 (+), 128.3 (+), 130.5 (+), 130.7 (+), 131.3 (+), 174.5 (–); HRMS (FAB^+) calcd for $C_{20}H_{31}O_4$ [$(M–H)^+$] 335.2222, found 335.2222.

Conflicts of interest

There are no conflicts to declare.

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