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Enantioselective Synthesis of *7(S)*-Hydroxydocosahexaenoic Acid, a Brain-Specific Endogenous Ligand for PPARα

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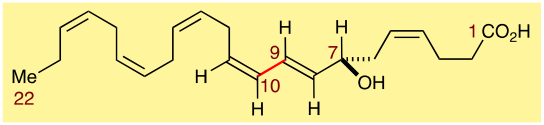
Supporting Information Placeholder

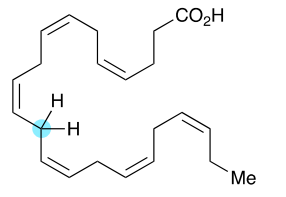
ABSTRACT: We report the first total synthesis of the polyunsaturated fatty acid 7-hydroxydocosahexaenoic acid (7-HDHA) in racemic form, and the enantioselective synthesis of 7-*(S)*-HDHA. Both syntheses follow a convergent approach that unites the C1-C9 and C10-C22 fragments using a Sonogashira coupling and a Boland reduction as key steps. These syntheses enabled the unambiguous characterization of this natural product for the first time, and helped establish 7*(S)*-HDHA as the endogenous ligand for peroxisome proliferator-activated receptor alpha (PPARα) in the brain.



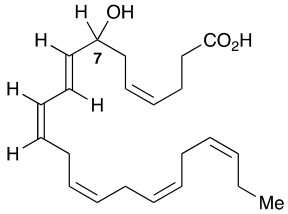
INTRODUCTION

Oxidative metabolites of polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA), have become attractive leads for the development of new therapeutics, primarily due to their anti-inflammatory effects.[1,2] Congeners of this family of natural products arise through progressive oxidation of the weak bis-allylic C-H bonds (BD = 72.7 kcal/mol),[2a] resulting in the simultaneous installation of hydroxyl groups and double bond conjugation. Representative examples[3] of this family, with increasing oxidation states, include 7-HDHA (**2**), maresin 1 (**3**) and resolvin D1 (**4**) (Figure 1).

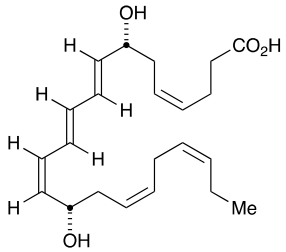
Figure 1. Docosahexaenoic acid (DHA, **1**) and some of its oxidation products, 7-HDHA (**2**) maresin 1 (**3**) and resolvin D1 (**4**) are biologically active metabolites with therapeutic potential.



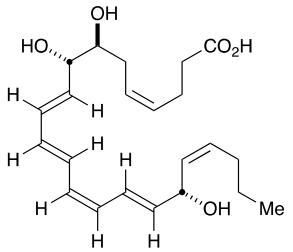
docosahexaenoic acid (DHA, **1**)



7-hydroxydocosahexaenoic acid (7-HDHA, **2**)



maresin 1 (**3**)



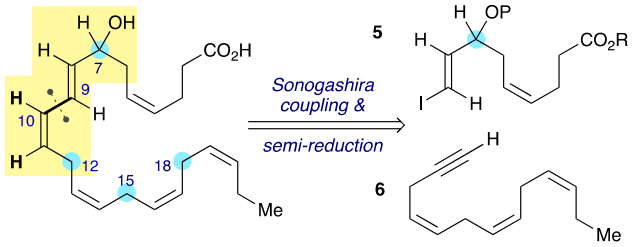
resolvin D1 (**4**)

Besides exerting regulatory effects on metabolism and inflammation, PUFAs are also implicated in signalling pathways in the brain.[4] It has been shown that activation of the peroxisome proliferator-activated receptor alpha (PPARα) in adult hippocampal neural stem cells promotes neurogenesis.[5] Therefore, the identification of high affinity brain-specific ligands for PPARα could serve as a lead for the development of treatment for neurodegenerative diseases such as Alzheimer's. A recent study identified 7-HDHA as a selective, brain-specific endogenous ligand for PPARα,[6] however, structural assignment of 7-HDHA relied on HPLC-MS-MS and therefore remained inconclusive. In addition, the limited supply, prohibitive cost and questionable purity of commercial 7-HDHA prevented follow-up studies. To alleviate this supply problem, we embarked on the first synthesis of *rac*-7-HDHA and enantiopure 7*(S)*-HDHA. These syntheses enabled the unambiguous identification of 7*(S)*-HDHA as a potent and selective ligand for brain PPARα and serve as a possible starting point for the development of therapeutics for neurodegenerative diseases.

RESULTS AND DISCUSSION

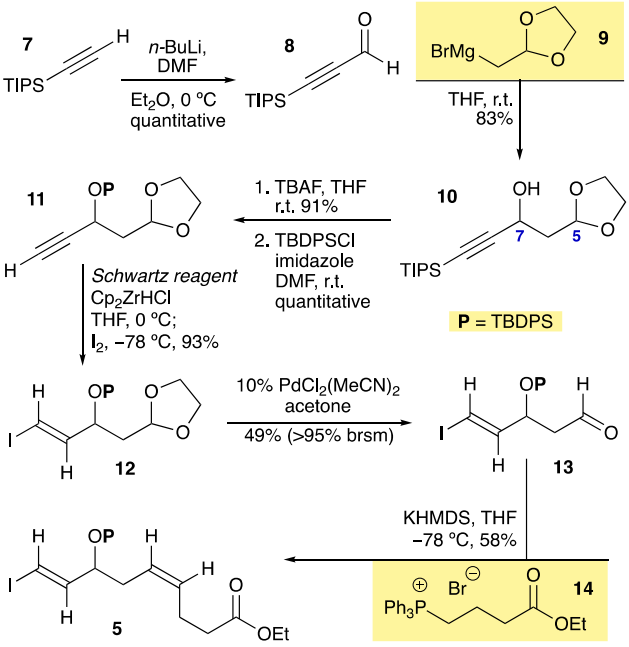
The synthetic challenge posed by 7–HDHA consists primarily of establishing the conjugated *trans,cis*-diene at C8–C11, the allylic hydroxyl function at C7, and the skipped tetraene spanning C10 to C20 (Scheme 1). An additional concern in this synthesis is the three doubly allylic methylene groups (at C12, C15 and C18), which render the target and some intermediates sensitive to oxidation. Retrosynthetic disconnection of 7–HDHA about the C9–C10 sigma bond results in two fragments of similar complexity, which can be joined in the forward sense through a Sonogashira cross-coupling of a *trans*-alkenyl iodide and a terminal alkyne, and *cis*-selective semi-hydrogenation of the resulting conjugated enyne.

Scheme 1. Retrosynthetic analysis of 7-HDHA



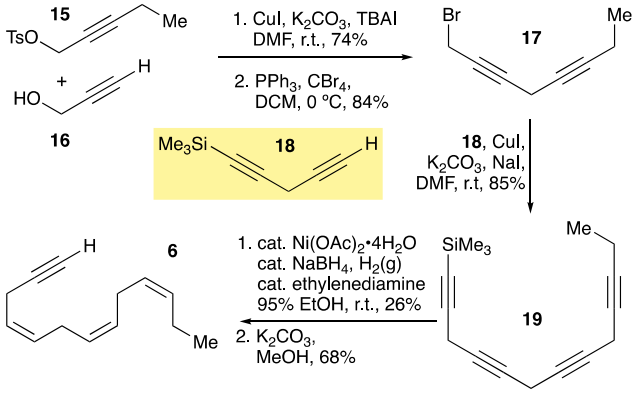
Our first-pass racemic synthesis of 7–HDHA began with the preparation of the C1–C9 fragment **5** (Scheme 2). Formylation of commercially available TIPS-mono-protected acetylene **7** by deprotonation with *n*-BuLi and quenching with DMF provided aldehyde **8** in quantitative yield. Installation of acetal protected aldehyde at the C5 position and the secondary alcohol at the C7 position in **10** was achieved by addition of Grignard **9**[7] to aldehyde **8** in 83% yield. Removal of the acetylenic silyl protecting group by treatment with TBAF, and protection of the propargylic alcohol furnished acetal **11** in high yield. Protection of the alcohol became necessary because all attempts to remove the acetal group at C5 in compound **10** inevitably led to elimination (not shown). Regioselective hydrozirconation[8] followed by an iodine quench provided **12**, with the required *trans*-alkenyl iodide at the eventual C8–C9 position. Unexpectedly, removal of the acetal moiety in **12** proved challenging using standard methods and largely resulted in decomposition. The required aldehyde **13** could be revealed using palladium as a mild Lewis acid[9] in the presence of acetone. Although uncommon, the use of Pd(II) for acetal deprotection provided a high yield of the product (based on recovered starting material), while the use of other Lewis acids (e.g. $FeCl_3$) resulted in significant decomposition. Wittig reaction with the unstabilized ylide[10] derived from **14** provided the C4–C5 *cis*-alkene **5** as expected.

Scheme 2. Synthesis of C1-C9 fragment **5**.



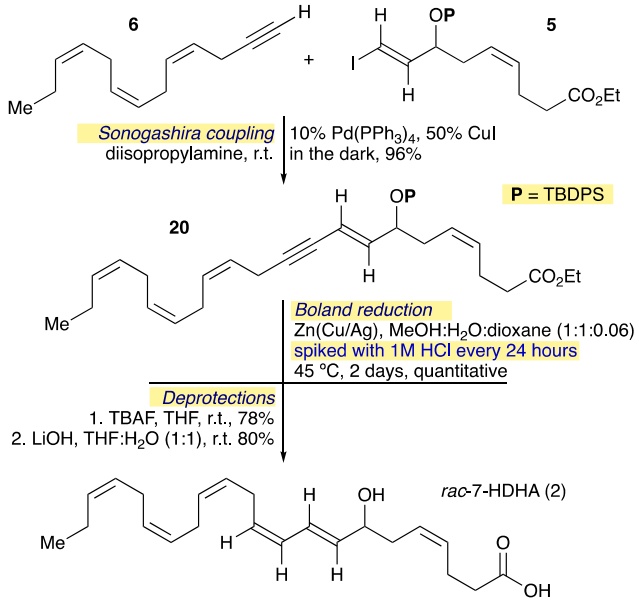
Preparation of the C10–C22 fragment **6** began with the copper mediated coupling of tosylated 2-pentyn-1-ol **15** with propargylic alcohol **16**,[11] giving the intermediate alcohol in 74% yield (Scheme 3). This alcohol was then converted to the corresponding bromide **17** which was then coupled with the commercially available skipped diyne **18** in a similar manner, providing the silyl-protected tetraalkyne **19** in good yield. The selective hydrogenation of skipped polyalkynes to the corresponding skipped alkenes characteristic of poly-unsaturated fatty acids, remains very challenging.[12] Commonly used methods, such as hydrogenation with Lindlar's catalyst and the Rosenmund reduction provided no conversion in our hands. Luckily, the P-2 nickel system[13] furnished the desired all-*cis* skipped triene in a modest 26% yield, supplying sufficient material to continue with the synthesis. Removal of the trimethylsilyl group was achieved under standard conditions to furnish alkyne **6.**

Scheme 3. Synthesis of C10-C22 fragment **6**.



To complete the synthesis, we united the C1–C9 and the C10–C22 fragments using a Sonogashira coupling[14] (Scheme 4). The critical step in this final sequence involved stereoselective semi-reduction of the conjugated enyne **20** spanning C8–C11. We elected to use Boland's method[15] over others, such as the Lindlar reduction, because it reliably provides the *cis*-configured semi-reduction product. Addition of dioxane to the usual solvent mixture consisting of MeOH and water was necessary to solubilize the highly lipophilic substrate. Interestingly, we found that the progress of this reaction stopped periodically, however activity could be rescued by spiking the reaction mixture with a few drops of aqueous 1M HCl every 24h. Finally, removal of the TBDPS protecting group using TBAF, and hydrolysis of the ethyl ester provided the desired (±) 7–HDHA **2**. To the best of our knowledge this is the first synthesis of this natural product. Curiously, no spectral data for this compound has been reported and we therefore fully characterized this synthetic sample using an array of NMR techniques, confirming its structure (See SI for full assignment and details).

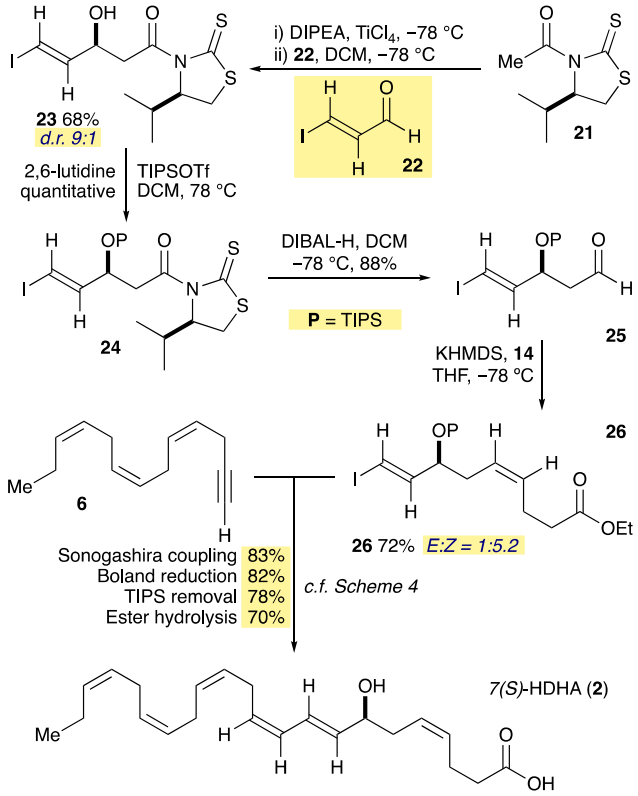
Scheme 4. Cross-coupling of fragments **5** and **6**, and completion of the total synthesis of (±)7–HDHA.



Chiral HPLC separation of (±)-7-HDHA into individual enantiomers identified 7*(S)*–HDHA as the endogenous ligand for PPARα and therefore this became our next target.[6] Our first synthesis of (±)-7-HDHA revealed a number of problems with the preparation of the C1-C9 fragment **5**, prompting a revised approach. The unanticipated use of a Pd(II) catalyst in high loads to reveal the C5 aldehyde, and the stoichiometric use of Schwartz's reagent were of particular concern. Furthermore, the propensity of the C7 alcohol to undergo elimination prompted us to seek an alternative approach to the installation of this group. These issues were readily addressed with a new strategy that also allowed the enantioselective synthesis of 7*(S)*–HDHA.

The synthesis began with a titanium mediated[16] Nagao-Fujita acetate aldol reaction[17] between *(R)*–acetyl thiazolidinethione **21** and *β*-iodoacrolein **22**,[18] providing aldol **23** as the major adduct[19] in 68% yield and with greater than 9:1 diastereoselectivity (Scheme 5). It is worth noting that a particular challenge with this reaction is the instability of *trans*-iodoacrolein **22**, which decomposes readily when neat. TIPS-protection of the secondary alcohol in **23** furnished silyl ether **24**, and reductive cleavage of the chiral auxiliary with DIBAL-H provided aldehyde **25** in 88% overall yield. Wittig reaction between aldehyde **25** and the phosphorane derived from **14** as before (c.f. Scheme 2) gave the *cis*-alkene **26** in good yield and greater than 5:1 selectivity for the desired geometric isomer. The presumptive minor *trans*-isomer (not shown) was separated to avoid complications at a later stage. Completion of the synthesis consisted of Sonogashira coupling of **6** and **26**, Boland reduction, and deprotections as before (c.f. Scheme 4), to furnish *7(S)*-HDHA for the first time.

Scheme 5. Enantioselective synthesis of *7(S)*-HDHA.



CONCLUSIONS

We have completed the first total synthesis of the polyunsaturated fatty acid 7-HDHA in racemic and enantioselective forms using a convergent approach. Our racemic synthesis proved to have some liabilities but nevertheless enabled the identification of the active enantiomer, allowed full characterization of this low-abundance natural product for the first time, and provided insights for the eventual enantioselective synthesis of 7*(S)*-HDHA. Our enantioselective approach provided sufficient amounts of 7*(S)*-HDHA for further biological studies.

EXPERIMENTAL SECTION

General. All reactions were conducted in flame or oven-dried glassware under an atmosphere of argon using anhydrous solvents unless specified otherwise. Tetrahydrofuran (THF), diethylether (Et_2O), dichloromethane (DCM) and toluene were dried using an INERT® PureSolv solvent purification system. Commercial reagents were used as received. Thin-layer chromatography was performed on SiliCycle® silica gel 60 F254 plates. Visualization was carried out using UV light (254 nm) and/or $KMnO_4$, $(NH_4)_2Ce(NO_3)_6$, vanillin, or anisaldehyde stains. Flash column chromatography[20] was carried out using SiliCycle® Sila*Flash*® silica gel (230–400 mesh, 40-63 μ, 60º A pore size). Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. ^{1}H–NMR and ^{13}C–NMR spectra were recorded on a Bruker 400 AV, Bruker DRX 600 or Bruker 300 AV spectrometer in chloroform-d (99.8 % deuterated). Spectra recorded using chloroform were calibrated to 7.26 ppm ^{1}H and 77.16 ppm ^{13}C. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), sext (sextet), sept (septet), td (triplet of doublets), dt (doublet of triplets), dd (doublet of doublets), ddt (doublet of doublet of triplets),[21] dddd (doublet of doublet of doublet of doublets),[21] m (multiplet) and br

(broad). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) using AlphaPlatinum ATR, Bruker, diamond crystal FT-IR instrument. High-resolution mass spectroscopy (HRMS) was performed on a JEOL AccuTOF Plus 4G model JMS-T 1000LP mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source; or an Agilent 6538 Q-TOF mass spectrometer equipped with an Agilent 1200 HPLC and a ESI ion source. Structural assignments were made with additional information from COSY, HSQC, HMBC, TOCSY, and NOESY experiments

1-(triisopropylsilyl)-1-propynal (8). A 200 mL round-bottom flask was charged with **7** (5.00 g, 27.42 mmol, 1.0 equiv.) in 30 mL of dry Et_2O and equipped with a stir bar. The solution was cooled to 0 °C and *n*–BuLi (1.6 M in hexane, 18.85 mL, 30.16 mmol, 1.1 equiv.) was added dropwise to it, the reaction was allowed to stir at 0 °C for 30 min. DMF (8.5 mL, 109.7 mmol, 4.0 equiv.) in 20 mL of Et_2O was then added dropwise to the reaction mixture at 0 °C. The reaction stirring was continued at 0 °C for two hours and finally quenched at 0 °C by slow addition of 1M HCl until a slightly acidic pH (5–6) was reached. After an hour of stirring at room temperature, the organic phase was separated, and the aqueous phase was extracted with 150 mL of ether. The organic layers were combined, washed with 100 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (10:90) as eluent to afford **8** as a pale-yellow oil (5.73 g, 99% yield). The ^{1}H-NMR and ^{13}C-NMR data is in accordance with that previously reported in the literature.[22] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 1.13-1.09 (m, 21H); **^{13}C{H}-NMR** (100 MHz, $CDCl_3$) δ 176.8, 104.6, 101.1, 18.5, 11.1.

1-(1,3-dioxolan-2-yl)-4-(triisopropylsilyl)but-3-yn-2-ol (10). A 200 mL round-bottom flask equipped with a condenser and a stir bar was charged with Mg turnings (458.5 mg, 19.00 mmol, 4.0 equiv.) and 20 mL of THF, which was followed by the addition of 2-(bromomethyl)-1,3-dioxolane (1.59 g, 9.5 mmol, 2.0 equiv.) and a small crystal of I_2. The reaction mixture was stirred for two hours at room temperature, then aldehyde **8** (1.0 g, 4.75 mmol, 1.0 equiv.) in 5 mL of THF was added dropwise to the Grignard reagent **9**. The reaction mixture was stirred at room temperature overnight and then cooled to 0 °C. Water (20 mL) were added dropwise to the reaction, followed by the addition of saturated aq. NH_4Cl. The organic phase was separated and the aqueous phase was extracted with ether (3 x 25 mL). The organic layers were combined and washed with 50 mL of brine and dried over $MgSO_4$, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography using ethyl acetate and hexane (30:70) as eluent to afford **10** as a colourless oil (1.18 g, 83% yield). **^{1}H-NMR** (300 MHz, $CDCl_3$), δ 5.17 (dd, *J* = 5.43 Hz, 4.41 Hz, 1H), 4.66 (m, 1H), 4.03-3.86 (m, 4H), 2.89 (d, *J* = 4.89 Hz, 1H), 2.21-2.02 (m, 2H), 1.07-1.05 (m, 20H); **^{13}C{H}-NMR** (75 MHz, $CDCl_3$), δ 107.6, 102.7, 85.8, 64.9, 59.6, 41.1, 18.7, 11.2; **HRMS (**DART**)** *m/z*: **[**$M+NH_4]^+$ calcd for $C_{16}H_{34}O_3SiN$ 316.2302; found 316.2310; **IR** *υ* = 3454, 2892, 2867, 2149, 1462, 1368, 1255, 1072 cm^{-1}.

((1-(1,3-dioxolan-2-yl)but-3-yn-2-yl)oxy)(*tert*-butyl)diphenylsilane (11). *Step 1:* A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with alcohol **10** (500.0 mg, 1.68 mmol, 1.0 equiv.) in 20 mL of THF. TBAF (483.3 mg, 1.85 mmol, 1.1 equiv.) was then added portion-wise. The mixture was stirred at room temperature for three hours. The reaction mixture was then concentrated under vacuum and the resulting residue was dissolved in 30 mL of ethyl acetate. This organic phase was then washed with 30 mL of brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (50:50) as eluent to afford the intermediate alcohol (not shown) as a colourless oil (217.13 mg, 91% yield). The ^{1}H-NMR and ^{13}C-NMR data is in accordance with that previously reported.[23] **^{1}H-NMR** (300 MHz, $CDCl_3$), δ 5.16 (dd, *J* = 4.86 Hz, 4.68 Hz, 1H), 4.67 (m, 1H), 4.05-3.87 (m, 4H), 3.07 (d, *J* = 5.34 Hz, 1H), 2.48 (d, *J* = 2.22 Hz, 1H), 2.22-2.04 (m, 2H); **^{13}C{H}-NMR** (75 MHz, $CDCl_3$), δ 102.5, 83.9, 73.2, 65.0, 58.9, 40.5; **IR** *υ* = 3405, 2966, 2891, 2891, 2185, 1411, 1303, 1134, 1065, 1019 cm^{-1}.

Step 2: A 25 mL round-bottom flask equipped with a stir bar was charged with the aforementioned alcohol (214.0 mg, 1.51 mmol, 1.0 equiv.), imidazole (257.3 mg, 3.78 mmol, 2.5 equiv.) and 5 mL of DMF. TBDPSCl (496.23 mg, 1.81 mmol, 1.2 equiv.) in 2 mL of DMF was then added to the reaction mixture dropwise at room temperature and the reaction was stirred overnight. Next, the mixture was diluted with 15 mL of Et_2O, and 10 mL of water was added. The organic phase was separated, and the aqueous phase was extracted with ether (3 x 20 mL). The organic layers were combined, washed with 35 mL of brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was purified by flash column chromatography using ethyl acetate and hexane (20:80) as eluent to afford alkyne **11** as a colourless oil (570.20 mg, 99% yield); **^{1}H-NMR** (600 MHz, $CDCl_3$), δ 7.75 (d, *J* = 6.72 Hz, 2H), 7.70 (d, *J* = 7.35 Hz, 2H), 7.44-7.36 (m, 6H), 5.02 (t, *J* = 5.1 Hz, 1H), 4.57 (td, *J* = 6.78 Hz, 1.92 Hz, 1H), 3.88-3.74 (m, 4H), 2.32 (d, *J* = 1.92 Hz, 1H), 2.10-2.03 (m, 2H), 1.08 (s, 9H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 136.2, 136.1, 133.5, 129.9, 129.8, 127.7, 127.5, 101.7, 84.3, 73.5, 64.9, 64.8, 60.7, 42.9, 27.1, 19.4; **HRMS** (DART) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{29}O_3Si$ 381.1880; found 381.1885; **IR** *υ* = 2957, 2929, 2889, 2556, 1463, 1421, 1361, 1138, 1086, 1058 cm^{-1}.

(*E*)-((1-(1,3-dioxolan-2-yl)-4-iodobut-3-en-2-yl)oxy)(*tert*-butyl)diphenylsilane (12). A 25 mL round-bottom flask equipped with a magnetic stir bar was charged with Cp_2ZrCl_2 (602.16 mg, 2.06 mmol, 2.0 equiv.) and 2.5 mL of THF, and resulting solution was cooled to 0 °C. A DIBAL-H solution (1.0 M in toluene, 1.85 mL, 1.85 mmol, 1.8 equiv.) was added dropwise into the reaction flask. The reaction was stirred for 30 minutes and then a solution of alkyne **11** (392.2 mg, 1.03 mmol, 1.0 equiv. in 1.5 mL of THF) was added dropwise to the reaction mixture at 0 °C. After one hour of stirring, the reaction was cooled to −78 °C and a solution of I_2 (522.85 mg, 2.06 mmol, 2.0 equiv. in 1.5 mL of THF) was added dropwise very slowly to the reaction mixture. After 20 minutes, the reaction was quenched with 1 M HCl. The organic phase was separated, and the aqueous phase was extracted with ether (3 x 20 mL). The organic layers were combined, washed successively with saturated aq. $Na_2S_2O_3$ (30 mL), $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was purified by flash column chromatography using ethyl acetate and hexane (5:95) as eluent to afford alkenyl iodide **12** as a colourless oil (485.5 mg, 93% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$), δ 7.66-7.61 (m, 4H), 7.43-7.36 (m, 6H), 6.48 (dd, *J* = 14.44 Hz, 7.40 Hz, 1H), 5.88 (dd, *J* =14.24 Hz, 0.84 Hz, 1H), 4.87 (t, *J* = 5.16 Hz, 1H), 4.31 (q, *J* = 6.56 Hz, 1H), 3.87-3.72 (m, 4H), 1.92 (m, 1H), 1.80 (m, 1H), 1.05 (s, 9H); **^{13}C{H}-NMR** (100 MHz, $CDCl_3$), δ 147.6, 135.9,

133.6, 129.8, 127.6, 101.5, 77.9, 73.0, 64.7, 64.6, 41.7, 26.9, 19.4; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{29}IO_3SiNa$ 531.0823; found 531.0816; **IR** υ = 2958, 2941, 2886, 1607, 1471, 1427, 1137, 1110, 947 cm^{-1}.

(*E*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-iodopent-4-enal (13). A 50 mL round-bottom equipped with a magnetic stirring bar was charged with 20 mL of acetone. Acetal **12** (50.00 mg, 0.1 mmol, 1.0 equiv.) was then added to the flask and stirred for 5 min followed by the addition of $PdCl_2(MeCN)_2$ (2.60 mg, 0.01 mmol, 0.10 equiv.). The reaction mixture was stirred at room temperature, in the dark for two days. The solvent was then removed using rotary evaporator, and the residual mixture was dissolved in 5 mL of Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using hexane and toluene (10:90) as eluent to afford **13** as a colourless oil (22.75 mg, 49%, 98% brsm), whereas 25 mg (50%) of starting material **12** was recovered. **^{1}H-NMR** (300 MHz, $CDCl_3$), δ 9.67 (t, *J* = 2.19 Hz, 1H), 7.65-7.60 (m, 4H), 7.45-7.37 (m, 6H), 6.54 (dd, *J* = 14.48 Hz, 6.57 Hz, 1H), 6.12 (dd, *J* = 14.46 Hz, 0.99 Hz, 1H), 4.58 (q, *J* = 5.73 Hz, 1H), 2.59-2.44 (m, 2H), 1.05 (s, 9H); **^{13}C{H}-NMR** (75 MHz, $CDCl_3$), δ 200.3, 146.4, 135.9, 133.1, 130.2, 127.9, 78.7, 71.8, 50.4, 27.0, 19.4; **HRMS** (DART) *m/z*: $[M+NH_4]^+$ calcd for $C_{21}H_{29}IO_2SiN$ 482.1006; found 482.1005; **IR** υ = 3070, 2957, 2930, 2857, 1724, 1607, 1427, 1361, 1104, 1071, 997 cm^{-1}.

Ethyl (4*Z*,8*E*)-7-((*tert*-butyldiphenylsilyl)oxy)-9-iodonona-4,8-dienoate (5). A 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with Wittig salt **14**[24] (667.73 mg, 1.46 mmol, 4.3 equiv.) in 3 mL of THF, which was then cooled to -78 °C. A KHMDS solution (0.5 M in toluene, 2.72 mL, 1.36 mmol, 4.0 equiv.) was added dropwise in the reaction mixture, resulting in a yellow suspension. After one hour of stirring at -78 °C, a solution of aldehyde 13 (106.0 mg, 0.34 mmol, 1.0 equiv.) in 3 mL of THF was then added dropwise (very slowly) to the reaction mixture. The reaction mixture was stirred for an hour at -78 °C and quenched by dropwise addition of sat. aq. NH_4Cl and diluted with Et_2O. The organic phase was separated and the aqueous phase was extracted with ether (35 mL x 3). The organic layers were combined, washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford **5** as a colourless oil (110.84 mg, 58% yield). The geometry of the newly installed double bond was confirmed using a homo-decoupling experiment (see Figure S8 in the Supporting Information) ; **^{1}H-NMR** (400 MHz, $CDCl_3$), δ 7.67-7.61 (m, 4H), 7.44-7.35 (m, 6H), 6.47 (dd, *J* = 14.40 Hz, 6.56 Hz, 1H), 5.98 (dd, *J* = 14.40 Hz, 1.04 Hz, 1H), 5.42-5.28 (m, 2H), 4.14-4.08 (m, 3H), 2.28-2.16 (m, 6H), 1.25 (t, *J* = 7.12 Hz, 3H), 1.06 (s, 9H); **^{13}C{H}-NMR** (100 MHz, $CDCl_3$), δ 173.2, 147.9, 136.0, 133.9, 133.6, 130.4, 129.9, 127.7, 125.4, 75.7, 60.5, 35.2, 34.3, 27.1, 22.9, 19.5, 14.0; **HRMS** (DART) *m/z*: $[M+NH_4]^+$ calcd for $C_{27}H_{39}IO_3SiN$ 580.1738; found 580.1732; **IR** υ = 2958, 2930, 2857, 1734, 1606, 1427, 1362, 1161, 1105, 1076, 941 cm^{-1}.

Pent-2-yn-1-yl 4-methylbenzenesulfonate (15) In a 100 mL round-bottom flask, 2-pentynol (1.00 g, 11.89 mmol, 1.0 equiv.) was dissolved in 25 mL Et_2O. Tosyl chloride (2.83 g, 14.86 mmol, 1.25 equiv.) and potassium hydroxide (3.34 g, 59.45 mmol, 5.0 equiv.) were then added into the solution. After the mixture was stirred at room temperature overnight, 20 mL Et_2O was added into the reaction mixture. The reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine, dried over MgSO4, filtered and concentrated under reduced pressure to afford **15** as a pale-yellow oil (2.51 g, 89% yield), no further purification was needed. The ^{1}H-NMR and ^{13}C-NMR data is in accordance with that previously reported in the literature.[25] ^{1}H-NMR (400 MHz, CDCl3), δ 7.82 (d, *J* = 8.28 Hz, 2H), 7.34 (d, *J* = 8.22 Hz, 2H), 4.70 (t, *J* = 2.16 Hz, 2H), 2.45 (s, 3H), 2.12-2.06 (m, 2H), 1.02 (t, *J* = 7.52 Hz, 3H); **^{13}C{H}-NMR** (100 MHz, $CDCl_3$), δ 144.99, 133.60, 129.86, 128.29, 91.90, 71.35, 58.89, 21.78, 13.30, 12.49.

1-bromoocta-2,5-diyne (17). *Step 1:* In a 100 mL round-bottom flask equipped with a magnetic stirring bar, **15** (2.51 g, 10.53 mmol, 1.0 equiv.) was dissolved in 25 mL of DMF, and to this solution was added CuI (2.01 g, 10.53 mmol, 1.0 equiv.), K_2CO_3 (2.18 g, 15.80 mmol, 1.5 equiv.) and TBAI (3.89 g, 10.53 mmol, 1.0 equiv.). The reaction mixture was cooled to 0 °C and propargyl alcohol **16** (708.6 mg, 12.64 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. Next, the reaction mixture was cooled to 0 °C, 20 mL of cold water and 150 mL of saturated aq. NH_4Cl were added sequentially. The mixture was extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (30:70) as eluent to afford intermediate propargylic alcohol (not shown) as a yellow oil (816.20 mg, 74% yield). The ^{1}H-NMR and ^{13}C-NMR data is in accordance with that previously reported in the literature.[26] **^{1}H-NMR** (400 MHz, $CDCl_3$), δ 4.27 (m, 2H), 3.19 (m, 2H), 2.18 (m, 2H), 1.12 (t, J = 2.16 Hz, 3H); **^{13}C{H}-NMR** (100 MHz, $CDCl_3$), δ 82.6, 80.9, 78.5, 72.8, 51.4, 13.9, 12.4, 9.9.

Step 2: A 100 mL round-bottom flask equipped with a magnetic stirring bar was charged with the above intermediate alcohol (1.00 g, 8.19 mmol, 1.0 equiv.) and CBr_4 (2.99 g, 9.01 mmol, 1.1 equiv.) in 20 mL of DCM. A solution of PPh_3 (2.36 g, 9.01 mmol, 1.1 equiv.) in 10 mL of DCM was then added dropwise to the reaction mixture. After stirring overnight at room temperature, the solvent was removed by using a rotary evaporator, and the residual mixture was purified directly using flash chromatography with ethyl acetate and hexane (5:95) as eluent to afford **17** as a pale-yellow oil (1.27 g, 84% yield). The ^{1}H-NMR and ^{13}C-NMR data is in accordance with that previously reported in the literature.[27] **^{1}H-NMR** (600 MHz, $CDCl_3$), δ 3.92 (m, 2H), 3.21 (m, 2H), 2.17 (m, 2H), 1.12 (td, J = 7.44 Hz, 1.67 Hz, 3H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 82.8, 82.2, 75.4, 72.3, 14.9, 13.9, 12.5, 12.5, 10.2; **IR** υ = 2976, 2936, 2232, 1713, 1691, 1592, 1453, 1411, 1320, 1209, 1124 cm^{-1}.

Trimethyl(trideca-1,4,7,10-tetrayn-1-yl)silane (19). In a 200 mL round-bottom flask, bromide **17** (1.29 g, 6.87 mmol, 1.0 equiv.) was dissolved in 60 mL of DMF. To this solution was added CuI (1.99 g, 10.46 mmol, 1.5 equiv.), K_2CO_3 (1.93 g, 13.94 mmol, 2.0 equiv.), and NaI (1.57 g, 10.46 mmol, 1.5 equiv.). The reaction mixture was cooled to 0 °C and alkyne **18** (1.23 g, 9.06 mmol, 1.3 equiv.) was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. Next, the reaction mixture was cooled to 0 °C, 20 mL of cold water and 150 mL of saturated aq. NH_4Cl were added sequentially. The mixture was extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **19** as a red oil (1.43 g, 85% yield). The compound 19

was unstable on silica gel and therefore used in the next step immediately without further purification. Crude **^{1}H-NMR** (300 MHz, $CDCl_3$), δ 3.22 - 3.13 (m, 6H), 2.22 – 2.13 (m, 2H), 1.12 (t, *J* = 7.50 Hz, 3H), 0.9 (s, 9H).

(4*Z*,7*Z*,10*Z*)-trideca-4,7,10-trien-1-yne (6). *Step 1:* A 125 mL round-bottomed flask equipped with a magnetic stirring bar was charged with $Ni(OAc)_2.4H_2O$ (301.1 mg, 1.21 mmol, 0.20 equiv.). The flask was purged with H_2 gas three times by vacuum-H_2 cycle and 20 mL of 95% EtOH (all EtOH was freshly degassed by three freeze-pump-thaw cycles) was introduced into the flask under constant supply of H_2 gas. A solution of $NaBH_4$ (45.77 mg, 1.21 mmol, 0.20 equiv.) in 5 mL of 95% EtOH was added dropwise (reaction mixture turns black). After 30 minutes of stirring, ethylenediamine (109.4 mg, 1.82 mmol, 0.40 equiv.) in 1 mL of 95% EtOH was then added into the reaction mixture and a solution of compound **19** (1.46 g, 6.07 mmol, 1.0 equiv.) in 2 mL of 95% EtOH was introduced into the reaction mixture dropwise. The reaction flask was then sealed and equipped with an H_2 balloon and stirred overnight. The reaction mixture was filtered through a pad of Celite and rinsed with 20 mL of ether. The filtrate was concentrated under reduced pressure, and purified by flash chromatography with pentane as eluent to afford the skipped alkene intermediate (not shown) as a colourless oil (388.50 mg, 26% yield); **^{1}H-NMR** (600 MHz, $CDCl_3$), δ 5.48-5.29 (m, 6H), 3.02 (d, J = 4.74 Hz, 2H), 2.84-2.79 (m, 4H), 2.06 (m, 2H), 0.98 (t, J = 7.56 Hz, 3H), 0.15 (s, 9H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 132.3, 130.0, 129.1, 127.4, 127.1, 124.4, 105.2, 84.5, 25.7, 25.7, 20.7, 18.6, 14.4, 0.2; the intact protonated molecular ion ($M+H^+$) is not observed by DART, nor is the molecular ion (M^+) observed in the EI spectrum, thus no HRMS data is obtained for this compound; **IR** υ = 3012, 2962, 2176, 1442, 1249, 1028, 841 cm^{-1}.

Step 2: A 25 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 5 mL of THF/MeOH (1:1), the skipped alkene intermediate obtained from step 1 (100.0 mg, 0.41 mmol, 1.0 equiv.), and K_2CO_3 (170.0 mg, 1.23 mmol, 3.0 equiv.). After the reaction mixture was stirred at room temperature for three hours, it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and purified directly by flash chromatography with pentane as eluent to afford **6** as a colourless oil (48.8 mg, 68% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$), δ 5.55-5.30 (m, 6H), 3.00 (m, 2H), 2.88-2.82 (m, 4H), 2.10 (pentet, J = 7.57 Hz, 2H), 2.01 (t, J = 2.72 Hz, 1H), 1.00 (t, J = 7.54 Hz, 3H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 132.4, 130.4, 129.3, 127.3, 127.1, 124.2, 82.8, 68.3, 25.8, 20.8, 17.1, 14.5; **HRMS** (DART) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{19}$ 175.1481; found 175.1480; **IR** υ = 3307, 3012, 2963, 2930, 2119, 1651, 1461, 1403, 1393, 1260, 1079, 1018, 910 cm^{-1}.

Ethyl (4*Z*,8*E*,13*Z*,16*Z*,19*Z*)-7-((*tert*-butyldiphenylsilyl)oxy) docosa-4,8,13,16,19-pentaen-10-ynoate (20). To a 10 mL round-bottomed flask equipped with a magnetic stirring bar was added 2 mL of freshly-distilled diisopropylamine, compound **5** (67.51 mg, 0.12 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (13.87 mg, 0.012 mmol, 0.10 equiv.). The resulting solution was stirred for 30 minutes, then CuI (11.43 mg, 0.06 mmol, 0.50 equiv.) and **6** (30.0 mg, 0.16 mmol, 1.3 equiv.) were added. After stirring overnight at room temperature, the reaction mixture was diluted with Et_2O, followed by addition of saturated aq. NH_4Cl. The aqueous layer was extracted with Et_2O (15 mL x 3). The organic layers were combined, washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford **20** as a colourless oil (69.9 mg, 96% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ 7.68 – 7.61 (m, 4H), 7.43 – 7.34 (m, 6H), 6.01 (dd, *J* = 15.84 Hz, 5.74 Hz, 1H), 5.54 (dd, *J* = 15.83 Hz, 1.51 Hz, 1H), 5.50 – 5.26 (m, 8H), 4.20 (m, 1H), 4.10 (q, *J* = 7.13 Hz, 2H), 3.09 – 3.08 (m, 2H), 2.86 – 2.80 (m, 4H), 2.28 – 2.04 (m, 8H), 1.24 (t, *J* = 7.13 Hz, 3H), 1.06 (s, 9H), 0.98 (t, *J* = 7.53 Hz, 3H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 173. 2, 144.0, 136.0, 136.0, 134.3, 133.8, 132.3, 130.0, 129.8, 129.8, 129.1, 127.7, 127.7, 127.4, 127.1, 125.8, 124.7, 110.0, 88.6, 78.7, 73.2, 60.4, 35.6, 34.2, 29.9, 27.2, 25.7, 22.9, 20.7, 18.5, 18.1, 14.4; **HRMS** (DART) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{53}O_3Si$ 609.3758; found 609.3761; **IR** υ = 3013, 2960, 2857, 1736, 1471, 1427, 1369, 1157, 1110, 1070, 955 cm^{-1}.

(±)7-HDHA (2). *Step 1: Alkylne Semi-reduction* 3.0 g of Zn dust was purified by washing sequentially with 1 M HCl twice, distilled water, EtOH, and Et_2O (the wash solutions were removed each time by filtration). The purified zinc dust was transferred into a 100 mL round-bottomed flask that was equipped with a magnetic stirring bar. Distilled water (30 ml) was added, and 300 mg of $Cu(OAc)_2{\cdot}H_2O$ was added to the vigorously stirred suspension. After 15 minutes of stirring, 300 mg of $AgNO_3$ was added to the suspension. After another 30 minutes stirring, the water was filtered off under strict argon atmosphere, the wet Zn(Cu/Ag) cake was washed sequentially with acetone and Et_2O, the solvents were removed each time by filtration. The fresh Zn(Cu/Ag) was then dried under vacuum.

The fresh Zn(Cu/Ag) was then transferred to a 100 mL argon-filled round-bottom flask and 50 mL of MeOH: H_2O (1:1) was added into the flask. A solution of compound **20** (150.0 mg, 0.25 mmol) in 1.5 mL of dioxane was added to the suspension of Zn(Cu/Ag). The reaction mixture was stirred at 45 °C (oil bath heating) for 6 hours, then 0.2 mL of 1 M HCl was added to the reaction mixture. After stirring overnight, another 0.2 mL of 1 M HCl was added to the reaction as progress of the reaction was found to have stalled (Aliquots were taken to check the consumption of **20** by ^{1}H-NMR). Until the reaction reached full conversion, 0.2 mL of 1 M HCl was added to the reaction mixture every 16 to 24 hours. After completion, the reaction mixture was filtered through Celite, the cake was thoroughly rinsed with 50 mL of MeOH and then 100 mL of Et_2O. The filtrate was concentrated under reduced pressure until most of the organic solvent was removed. The residual mixture was diluted with 100 mL of Et_2O, the organic layer was washed with water, then brine (50 mL x 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford *cis*-olefin intermediate (not shown) as a colourless oil (154.1 mg, 100% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$), δ 7.69 – 7.64 (m, 4H), 7.42 – 7.33 (m, 6H), 6.22 (dd, *J* = 15.11 Hz, 11.09 Hz, 1H), 5.89 (t, *J* = 10.82 Hz, 1H), 5.61 (dd, *J* = 15.12 Hz, 6.54 Hz, 1H), 5.41 – 5.28 (m, 9H), 4.23 (m, 1H), 4.11 (q, *J* = 7.14 Hz, 2H), 2.83 – 2.78 (m, 6H), 2.32 – 2.28 (m, 1H), 2.25 – 2.22 (m, 3H), 2.20 – 2.16 (m, 2H), 2.05 (m, 2H), 1.24 (t, *J* = 7.22 Hz, 3H), 1.07 (s, 9H), 0.97 (t, *J* = 7.53 Hz, 3H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 173. 2, 136.1, 136.1, 135.9, 134.5, 134.2, 132.2, 129.7, 129.7, 129.6, 128.8, 128.6, 128.3, 127.9, 127.6, 127.5, 127.2, 126.4, 125.4, 73.9, 60.4, 36.1, 34.3, 29.8, 27.2, 26.1, 25.8, 25.7, 23.0, 20.7, 19.5, 14.4; **HRMS** (DART) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{55}O_3Si$ 611.3915; found 611.3918; **IR** crystal υ = 3070, 3012, 2960, 2930, 2856, 1736, 1462, 1390, 1175, 1157, 1110 cm^{-1}.

Step 2: TBAF Deprotection A 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with the above cis-olefin intermediate (130.0 mg, 0.21 mmol, 1.0 equiv.) in 10 mL of THF. A solution of TBAF (1M in THF, 0.24 mL, 0.23 mmol, 1.1 equiv.) was added to the reaction mixture dropwise and stirred at room temperature overnight. Next, the reaction mixture was quenched by the addition of water, the aqueous layer was separated and extracted with ethyl acetate (25 mL x 3). The organic phase was then washed with 25 mL of brine, and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (15:85) as eluent to afford intermediate alcohol (not shown) as a colourless oil (61.4 mg, 78% yield); **^{1}H-NMR** (700 MHz, $CDCl_3$), δ 6.56 (dd, J = 15.07 Hz, 11.23 Hz, 1H), 6.02 – 5.99 (m, 1H), 5.73 (dd, J = 14.71 Hz, 6.44 Hz, 1H), 5.55 – 5.46 (m, 2H), 5.43 – 5.36 (m, 6H), 5.34 – 5.30 (m, 1H), 4.24 (m, 1H), 4.13 (q, J = 7.21 Hz, 2H), 2.97 (m, 2H), 2.85 (m, 2H), 2.81 (m, 2H), 2.42 – 2.33 (m, 6H), 2.08 (m, 2H), 1.25 (t, J = 7.03 Hz, 3H), 0.98 (t, J = 7.54 Hz, 3H); **^{13}C{H}-NMR** (150 MHz, $CDCl_3$), δ 173.4, 135.9, 132.2, 131.2, 130.5, 128.8, 128.2, 127.9, 127.8, 127.2, 126.3, 125.6, 72.0, 60.6, 35.6, 34.1, 26.3, 25.8, 25.7, 23.0, 20.7, 14.4, 14.4; **HRMS** (DART) *m/z*: $[M+NH_4]^+$ calcd for $C_{24}H_{40}O_3N$ 390.3002; found 390.3002; **IR** υ = 3433, 2968, 2942, 2252, 1735, 1647, 1446, 1418, 1375, 1180, 1038, 918 cm^{-1}.

Step 3: Ester Hydrolysis In 10 mL round-bottomed flask equipped with magnetic stir bar, the alcohol intermediate from Step 2 (41.0 mg, 0.11 mmol, 1.0 equiv.) was dissolved in 3 mL of H_2O: THF (1:1) and $LiOH.H_2O$ (39.5mg, 1.65 mmol, 15.0 equiv.) was then added to the flask. The reaction was stirred at room temperature overnight. The reaction mixture was then cooled to 0 °C and acidified by dropwise addition of 1 M HCl until pH = 5. The aqueous layer was then extracted with ethyl acetate (3 x 10 mL), and the combined organics were then washed over 15 mL of brine, and dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography using ethyl acetate and hexane (50:50) as eluent to afford (±)7–HDHA (**2**) as a colourless oil (30.4 mg, 80% yield); **^{1}H-NMR** (700 MHz, $CDCl_3$), δ 6.55 (dd, J = 15.13 Hz, 11.06 Hz, 1H), 6.00 (t, J = 10.86 Hz, 1H), 5.72 (dd, J = 15.16 Hz, 6.41 Hz, 1H), 5.53 (m, 1H), 5.48 (m, 1H), 5.43 – 5.35 (m, 6H), 5.32 (m, 1H), 4.25 (m, 1H), 2.97 (t, J = 6.93 Hz, 2H), 2.85 (t, J = 6.41 Hz, 2H), 2.81 (t, J = 6.51 Hz, 2H), 2.45 – 2.33 (m, 6H), 2.09 – 2.06 (m, 2H), 0.97 (t, J = 7.84 Hz, 3H), the carboxylic acid proton was not observed in this spectrum**;** **^{13}C{H}-NMR** (176 MHz, $CDCl_3$), δ 177.7, 135.6, 132.2, 130.9, 130.6, 128.8, 128.1, 127.9, 127.7, 127.1, 126.5, 125.7, 72.1, 35.5, 33.6, 26.2, 25.8, 25.7, 22.7, 20.7, 14.4; **HRMS** (DART) *m/z*: $[M-H]^-$calcd for $C_{22}H_{31}O_3$ 343.2268; found 343.2278; **IR** υ = 3617, 3005, 2943, 2310, 2292, 1733, 1652, 1437, 1418, 1375, 1038, 918 cm^{-1}.

(*S*,*E*)-3-hydroxy-5-iodo-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one (23). To a 100 mL round-bottom flask containing **21** (1.89 g, 9.31 mmol, 1.1 equiv.) was added 36 mL of DCM, the resulting yellow solution was cooled to –78 °C. $TiCl_4$ (1.00 M in DCM, 10.2 mL, 10.2 mmol, 1.2 equiv.) was added dropwise to the reaction mixture, resulting in a deep yellow solution. After five minutes of stirring, DIPEA (1.77 mL, 10.2 mmol, and 1.2 equiv.) was added carefully using a syringe pump over 30 min, and the resulting deep red solution was stirred for two hours at –78 °C. A solution of aldehyde **22** (1.54 g, 8.46 mmol, 1.0 equiv.) in DCM (12 mL) was added to the reaction mixture *via* syringe pump over 30 min. After 30 min of stirring at –78 °C the reaction was quenched by the dropwise addition of H_2O (50 ml). The flask was removed from the cooling bath and the system was allowed to warm to 23 °C while the mixture was rapidly stirring. The biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (2 × 20 mL) and then dried over Na_2SO_4. The dried solution was filtered and the filtrate was concentrated. The crude residue was purified by flash chromatography (silica gel, eluent: EtOAc:hexanes = 1 : 9) to afford *β*-hydroxyl amide **23** (2.23 g, 68%) as a yellow solid. (The *dr* ratio was found to be 9:1 in favour of desired product **23** from crude ^{1}H NMR. The minor isomer was separated using *gravity* column chromatography using EtOAc:hexanes = 10:90 to ensure proper separation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 14.5, 5.3 Hz, 1H), 6.48 (dd, *J* = 14.5, 1.4 Hz, 1H), 5.14 (ddd, *J* = 7.7, 6.3, 1.1 Hz, 1H), 4.70–4.56 (m, 1H), 3.68 (dd, *J* = 17.6, 3.1 Hz, 1H), 3.54 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.29 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.05 (dd, *J* = 11.5, 1.1 Hz, 2H), 2.35 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 203.2, 171.9, 145.9, 78.4, 71.5, 70.6, 44.4, 30.9, 30.9, 19.2, 17.9; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{17}INO_2S_2$ 385.9740; found 385.9732; **IR** *υ* = 2960, 2925, 1697, 1684, 1538, 1387, 1278, 1254, 1169, 1092, 1041 cm^{-1}.

(*S*,*E*)-5-iodo-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-((triisopropylsilyl)oxy)pent-4-en-1-one (24). A solution of alcohol **23** (1.0 g, 2.6 mmol, 1.0 equiv.) in anhydrous DCM (10 mL) was cooled to 0 °C, which was followed by dropwise addition of 2, 6-lutidine (0.52 mL, 5.2 mmol, 2.0 equiv.) and then TIPSOTf (0.76 mL, 3.9 mmol, 1.5 equiv.). After stirring for two hours, the reaction mixture was quenched with 25 mL of cold water at 0 °C and extracted with dichloromethane (3 x 25 mL). The organic layer was washed with water (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (8% ethyl acetate/hexanes) to give 1.4 g of desired product **24** as a colourless oil in quantitative yield. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 14.5, 6.8 Hz, 1H), 6.38 (d, *J* = 14.5 Hz, 1H), 5.07 (ddd, *J* = 7.8, 6.2, 1.3 Hz, 1H), 4.81 (q, *J* = 6.5 Hz, 1H), 3.62 (dd, *J* = 16.9, 6.4 Hz, 1H), 3.52 – 3.35 (m, 2H), 3.02 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.41 – 2.28 (m, *J* = 6.8 Hz, 1H), 1.11 – 0.99 (m, 24H), 0.97 (d, *J* = 7.0 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 202.9, 170.7, 148.2, 77.8, 72.4, 71.7, 46.3, 30.9, 30.8, 19.3, 18.2, 18.1, 17.9, 12.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{37}INO_2S_2Si$ 542.1074; found 542.1064; **IR** *υ* = 2960, 2942, 2865, 1696, 1607, 1464, 1361, 1254, 1173, 1153, 1093, 1038, 882 cm^{-1}.

(*S*,*E*)-5-iodo-3-((triisopropylsilyl)oxy)pent-4-enal (25). Ester **24** (1.4 g, 2.58 mmol, 1.0 equiv.) was dissolved in 50 mL of DCM and cooled to 0 °C. To this solution was added 2.84 mL (2.84 mmol, 1.1 equiv.) of DIBAL (1M in DCM) dropwise, and the reaction was stirred for 0.5 h at 0 °C. The reaction was quenched by the addition of saturated solution of K-Na tartrate in water (20 mL) at 0 °C and kept standing for 1 h to separate the two layers. After the layers were separated, the aqueous layer was washed with DCM (2 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo* and purified by chromatography (15% ethyl acetate/hexanes) over silica gel to afford 869 mg of **25** as colorless oil in 88% yield. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.79

(t, J = 2.1 Hz, 1H), 6.63 (dd, J = 14.5, 6.2 Hz, 1H), 6.42 (dd, J = 14.5, 1.2 Hz, 1H), 4.73 (qd, J = 5.9, 1.2 Hz, 1H), 2.69 – 2.60 (m, 2H), 1.04 (d, J = 4.4 Hz, 21H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 200.6, 147.6, 77.8, 71.3, 51.1, 18.1, 18.1, 12.4; **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{27}IO_2SiNa$ 405.0723; found 405.0717; **IR** υ = 2942, 2865, 2724, 1724, 1607, 1462, 1164, 1106, 947 cm^{-1}.

Ethyl (*S*,4*Z*,8*E*)-9-iodo-7-((triisopropylsilyl)oxy)nona-4,8-dienoate (26). A 25 mL round-bottom oven-dried flask was equipped with a magnetic stirring bar and charged with Wittig salt **14** (1.23 g, 2.62 mmol, 2.0 equiv.) in 10 mL of THF was introduced into the flask, which was then cooled to -78 °C. A solution of KHMDS (0.5 M in toluene, 3.92 mL, 1.96 mmol, 1.5 equiv.) was added dropwise into the flask, resulting in a yellow suspension. After 1 hour of stirring at -78 °C, compound **25** (500.0 mg, 1.31 mmol, 1.0 equiv.) in 10 mL of THF was added dropwise (very slowly) to the reaction mixture. After one hour stirring at -78 °C, the reaction was quenched by addition of saturated aq. NH_4Cl solution (20 mL) and diluted with Et_2O (25 mL). The organic phase was separated, and the aqueous phase was extracted with ether (25 mL x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford the major isomer **26** as a colourless oil (452.0 mg, 72% yield). The identity of compound **26** was assigned by analogy to compound **5**, which differs only in the nature of the silyl protecting group. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.52 (dd, J = 14.4, 6.4 Hz, 1H), 6.21 (dd, J = 14.4, 1.1 Hz, 1H), 5.49 – 5.35 (m, 2H), 4.28 – 4.18 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.40 – 2.23 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 3.0 Hz, 21H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 173.2, 148.9, 130.3, 125.6, 76.2, 75.2, 60.5, 35.9, 34.3, 23.2, 18.2, 18.1, 14.4, 12.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{38}IO_3Si$ 481.1619; found 481.1629; **IR** υ = 2942, 2865, 1735, 1606, 1462, 1370, 1248, 1162, 1087, 1064, 943 cm^{-1}.

Ethyl (*S*,4*Z*,8*E*,14*Z*,17*Z*,20*Z*)-7-((triisopropylsilyl)oxy)tricosa-4,8,14,17,20-pentaen-10-ynoate (27). A 10 mL round-bottomed flask was equipped with a magnetic stir bar and charged with 2 mL of freshly-distilled diisopropylamine, **26** (250.0 mg, 0.52 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (60.1 mg, 0.052 mmol, 0.10 equiv.) were added to the flask. The resulting solution was stirred for 30 minutes. Next, CuI (49.5 mg, 0.26 mmol, 50 mol %) and 6 (117.5 mg, 0.62 mmol, 1.2 equiv.) were added. After stirring overnight at room temperature, the mixture was diluted with Et_2O, followed by addition of saturated aq. NH_4Cl. The aqueous layer was extracted with Et_2O (20 mL x 3). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford **27** as a colourless oil (234 mg, 83% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.01 (dd, J = 15.9, 5.9 Hz, 1H), 5.62 (dq, J = 15.9, 2.0 Hz, 1H), 5.51 – 5.24 (m, 8H), 4.34 – 4.22 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.08 (dd, J = 5.2, 2.3 Hz, 2H), 2.81 (dt, J = 13.5, 6.1 Hz, 4H), 2.42 – 2.22 (m, 6H), 2.13 – 2.01 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 2.9 Hz, 21H), 0.97 (t, J = 7.5 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 173.3, 145.0, 132.3, 129.8, 129.8, 129.1, 127.4, 127.1, 126.1, 124.7, 109.6, 88.5, 78.7, 72.7, 60.4, 36.3, 34.33, 25.7, 23.2, 20.7, 18.2, 18.1, 14.4, 12.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{55}O_3Si$ 527.3907; found 527.3915; **IR** υ = 2957, 2925, 2854, 2225, 2052, 1734, 1698, 1647, 1558, 1504, 1457, 1437, 1082, 1042 cm^{-1}.

Ethyl (*S*,4*Z*,8*E*,10*Z*,13*Z*,16*Z*,19*Z*)-7-((triisopropylsilyl)oxy) docosa-4,8,10,13,16,19-hexaenoate (28). 3.0 g of Zn dust was purified by washing sequentially with 1 M HCl twice, distilled water, EtOH, and Et_2O (the wash solutions were removed each time by filtration). The purified zinc dust was transferred into a 100 mL round-bottomed flask that was equipped with a magnetic stirring bar and filled with argon. Distilled water (30 mL) was added, and 300 mg of $Cu(OAc)_2{\cdot}H_2O$ was added to the vigorously stirred suspension. After 15 minutes of stirring, 300 mg of $AgNO_3$ was added to the suspension. After another 30 minutes stirring, the water was filtered off under strict argon atmosphere, the wet Zn(Cu/Ag) cake was washed sequentially with acetone and Et_2O, the solvents were removed each time by filtration. The fresh Zn(Cu/Ag) was then dried under vacuum.

The fresh Zn(Cu/Ag) was then transferred to a 100 mL argon-filled round-bottom flask. 50 mL of MeOH: H_2O (1:1) was added into the flask. Compound **27** (150.0 mg, 0.25 mmol) in 1.5 mL of dioxane was added to the suspension of Zn(Cu/Ag). The reaction mixture was stirred at 45 °C (oil bath heating) for six hours, then 0.2 mL of 1 M HCl was added to the reaction mixture. After stirring overnight, another 0.2 mL of 1 M HCl was added to the reaction. Aliquots were taken to check the consumption of **27** by ^{1}H-NMR. Until the reaction reached full conversion, 0.2 mL of 1 M HCl was added to the reaction mixture every 16 to 24 hours. After completion, the reaction mixture was filtered through Celite, the cake was thoroughly rinsed with 50 mL of MeOH and then 50 mL of Et_2O. The filtrate was concentrated under reduced pressure until most of the organic solvent was removed. The residual mixture was diluted with Et_2O, the organic layer was washed with water, then brine (25 mL x 2), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (5:95) as eluent to afford **28** as a colourless oil (124.0 mg, 82% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.52 – 6.40 (m, 1H), 6.06 – 5.92 (m, 1H), 5.66 (dd, J = 15.2, 6.4 Hz, 1H), 5.49 – 5.28 (m, 9H), 4.33 (q, J = 6.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.95 (ddd, J = 7.5, 4.8, 2.5 Hz, 2H), 2.88 – 2.74 (m, 4H), 2.42– 2.25 (m, 6H), 2.13–2.07 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.06 (q, J = 2.2 Hz, 21H), 0.97 (t, J = 7.5 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 173.1, 136.9, 132.0, 129.4, 129.4, 128.6, 128.5, 128.2, 127.8, 127.0, 126.5, 124.5, 72.9, 60.3, 36.6, 34.2, 26.0, 25.6, 25.5, 23.1, 20.6, 18.1, 18.1, 14.3, 12.4; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{57}IO_3Si$ 529.4067; found 529.4071; **IR** υ = 3031, 2925, 2865, 1738, 1699, 1647, 1558, 1463, 1372, 1246, 1158, 1084, 1063 cm^{-1}.

Ethyl (*S*,4*Z*,8*E*,10*Z*,13*Z*,16*Z*,19*Z*)-7-hydroxydocosa-4,8,10, 13,16,19-hexaenoate (29). A 25 mL round-bottom flask was equipped with a magnetic stirring bar, and charged with **28** (130.0 mg, 0.21 mmol, 1.0 equiv.) in 10 mL of THF, TBAF (1M in THF, 0.24 mL, 0.23 mmol, 1.1 equiv.) was then added to the solution drop-wise. The mixture was stirred at 0 °C for three hours. Next, the reaction was quenched by the addition of water, the aqueous layer was separated and extracted with ethyl acetate (3 x 20 mL). The organic phase was then washed over brine, and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (15:85) as eluent to afford **29** as a colourless oil (77.8 mg, 78% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.56 (dd, J = 15.2, 11.0 Hz, 1H), 6.02–5.99 (m, 1H), 5.73 (dd, J = 15.2, 6.3 Hz, 1H), 5.58 – 5.27 (m, 8H), 4.25–4.20

(m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.98–2.95 (m, 2H), 2.83 (dt, J = 16.1, 6.1 Hz, 4H), 2.47 – 2.27 (m, 6H), 2.11–2.03 (m, 2H), 1.94 (d, J = 4.1 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 173.4, 135.9, 135.7, 132.2, 131.2, 130.5, 130.4, 128.8, 128.2, 127.9, 127.9, 127.8, 127.2, 126.3, 125.6, 77.4, 77.1, 72.0, 60.6, 35.6, 34.1, 26.3, 26.2, 25.8, 25.7, 23.0, 20.7, 14.4, 14.4; **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{37}O_3$ 373.2727: found 373.2737; **IR** υ =3433, 2969, 2942, 2251, 1735, 1647, 1446, 1418, 1375, 1180, 1038 cm^{-1}.

7(*S*)-HDHA (2). In a 10 mL round-bottomed flask, **29** (70.0 mg, 0.19 mmol, 1.0 equiv.) was dissolved in 3 mL of H_2O:THF (1:1), $LiOH.H_2O$ (39.5 mg, 0.94 mmol, 5.0 equiv.) was then added to the flask. The reaction was stirred at room temperature for six hours. The reaction mixture was then cooled to 0 °C, 1 M HCl was then added dropwise until the aqueous layer was acidified to pH around 5. The aqueous layer was extracted with ethyl acetate (15 mL x 4). The organic phase was then washed over brine, and dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography using ethyl acetate and hexane (50:50) as eluent to afford 7(*S*)–HDHA (**2**) as colourless oil (45.3 mg, 70% yield). Chiral HPLC indicates that only 7(*S*)-HDHA is present in the sample without the other enantiomer. The chiral HPLC was performed on a Chiralpak-IA column (Amylose tris 3,5-dimethylphenyl-carbamate, 250 × 4.6 mm, Chiral Technologies Europe) and eluted with an isocratic elution of 45% mobile phase A (H_2O containing 0.1% formic acid), 55% mobile phase B (acetonitrile containing 0.1% formic acid). The temperatures of the column and sample compartments were maintained at 20 °C and 4 °C, respectively. Data were acquired at a wavelength of 230 nm using a DAD detector. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.55 (dd, J = 15.2, 11.0 Hz, 1H), 6.03 – 5.97 (m, 1H), 5.72 (dd, J = 15.2, 6.4 Hz, 1H), 5.55 – 5.27 (m, 8H), 4.26-4.19 (m, 1H), 2.98 (t, J = 6.7 Hz, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.93 – 2.80 (m, 4H), 2.43 – 2.34 (m, 6H), 2.09 – 2.06 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); **^{13}C{H}-NMR** (101 MHz, $CDCl_3$) δ 177.3, 135.7, 132.3, 130.8, 130.6, 128.8, 128.1, 127.9, 127.7, 127.2, 126.6, 125.7, 72.1, 35.5, 33.5, 26.3, 25.8, 25.7, 22.7, 20.7, 14.4; **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{32}O_3Na$ 367.2234; found 367.2244; **IR** υ = 3617, 3005, 2943, 2310, 2292, 1733, 1652, 1437, 1418, 1375, 1038, 918 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

COSY and HMBC Correlation tables of (±) 7-HDHA, spectral data of all synthesized compounds, and chiral HPLC data of 7(*S*)-HDHA and 7(*R*)-HDHA.

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