
# Stereoselective synthesis of (all-Z)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene


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# Stereoselective synthesis of (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene

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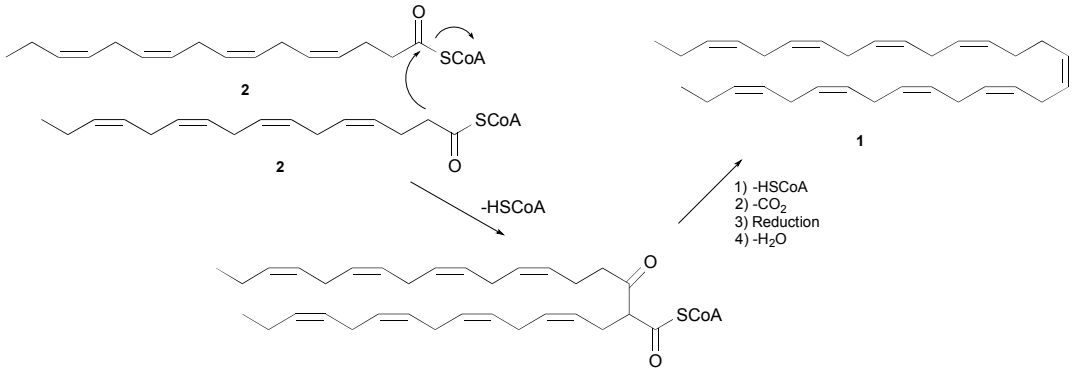
**ABSTRACT:** Several microorganisms produce small quantities of polyunsaturated hydrocarbons and such natural products are of interest. Starting from the ethyl ester of eicosapentaenoic acid, the total synthesis of the natural product (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene has been achieved in eight steps and 15% overall yield. The synthesis is based on a stereoselective Wittig reaction and confirms the all-*Z*-configuration of the nine double bonds in this highly unsaturated natural product.

## Introduction

Microbial fatty acid and lipid metabolisms are currently explored for the potential applications in bio-based production of hydrocarbons and other useful metabolites, such as polyunsaturated fatty acids (PUFAs).[1,2] Hydrocarbons are present in most microorganisms,[3] but the capability to produce long chain PUFAs, such as the ω-3 PUFAs eisocapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has mostly been reported for psychrophilic, piezophilic and some mesophilic (*Shewanella sp*.) bacteria phyla.[4,5] Recently it has been reported that the bacterial strains producing long-chain PUFAs are also characterized by the presence of a small amount of an uncommon polyolefin natural product, namely (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene (C31:9, **1**), see Scheme 1.[5-7] The positions and the *Z*-configuration of the nine double bonds as well as the structure of this un-branched very long-chain hydrocarbon (VLCH) **1** was assigned mainly on data obtained from FTIR- and MS-experiments.[5,7] Sukovich et al. discussed that the C31:9 lipid **1** may be biosynthesized *via* a head-to-head condensation pathway between two entities derived from (all-*Z*)-4,7,10,13-hexadecatetraenoic acid (**2**) (Scheme 1).[7,8]

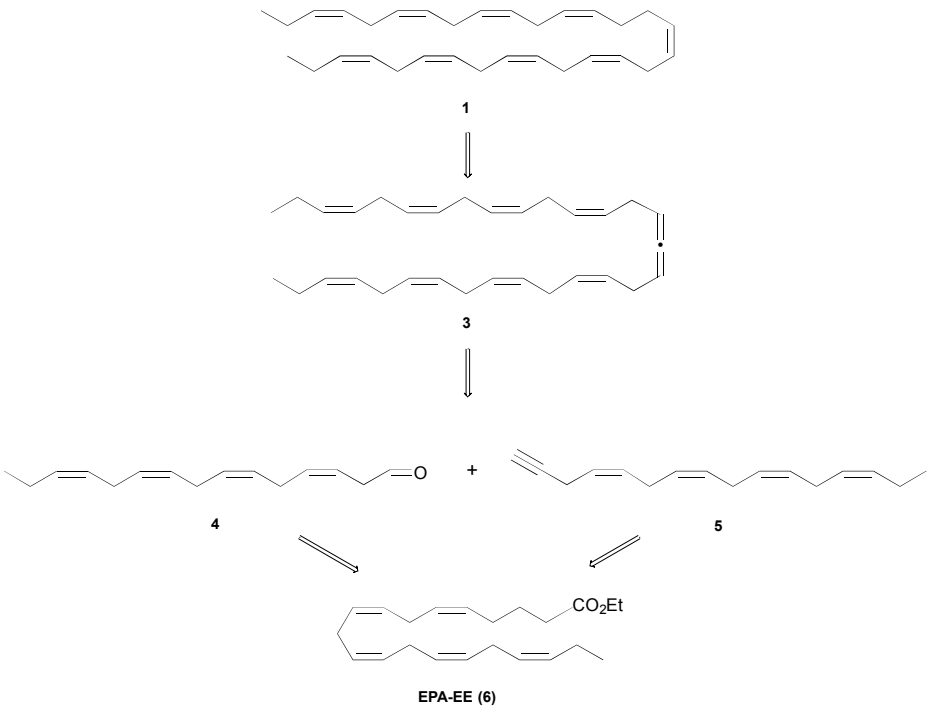



**Scheme 1** The proposed biosynthesis of the VLCH **1**.

As of today, no biochemical proof of this type of biosynthesis has been presented. Therefore, the geometry of the middle-chain double bond as well as the stereochemistry of the eight methylene interrupted *Z*-double bonds remains to be established by other evidence than the FTIR spectra. In addition, no biological data of the natural product **1** have been reported. Most likely the C31:9 natural product **1** is involved in cold adaptation mechanisms beneficial for the bacteria.[9] Hence, a stereoselective total synthesis of the natural occurring VLCH **1** is required both for the exact structure elucidation and for providing enough material for conducting biological studies. These reasons, together with our interest in the synthesis of PUFA-derived natural products,[10] motivated us to achieve the first total synthesis of **1**. These efforts are reported herein.

**Results and discussion**

Considering the latent symmetry present in the hydrocarbon **1** around the C15-C16 bond, we assumed that the target molecule **1** could be obtained by a stereoselective semi-reduction of the symmetric allene **3**. Of notice, the regiochemistry is of no concern since any partial *Z*-selective reduction of **3** should lead to the formation of **1**. Our retrosynthetic analysis of **1** is outlined in Scheme 2.

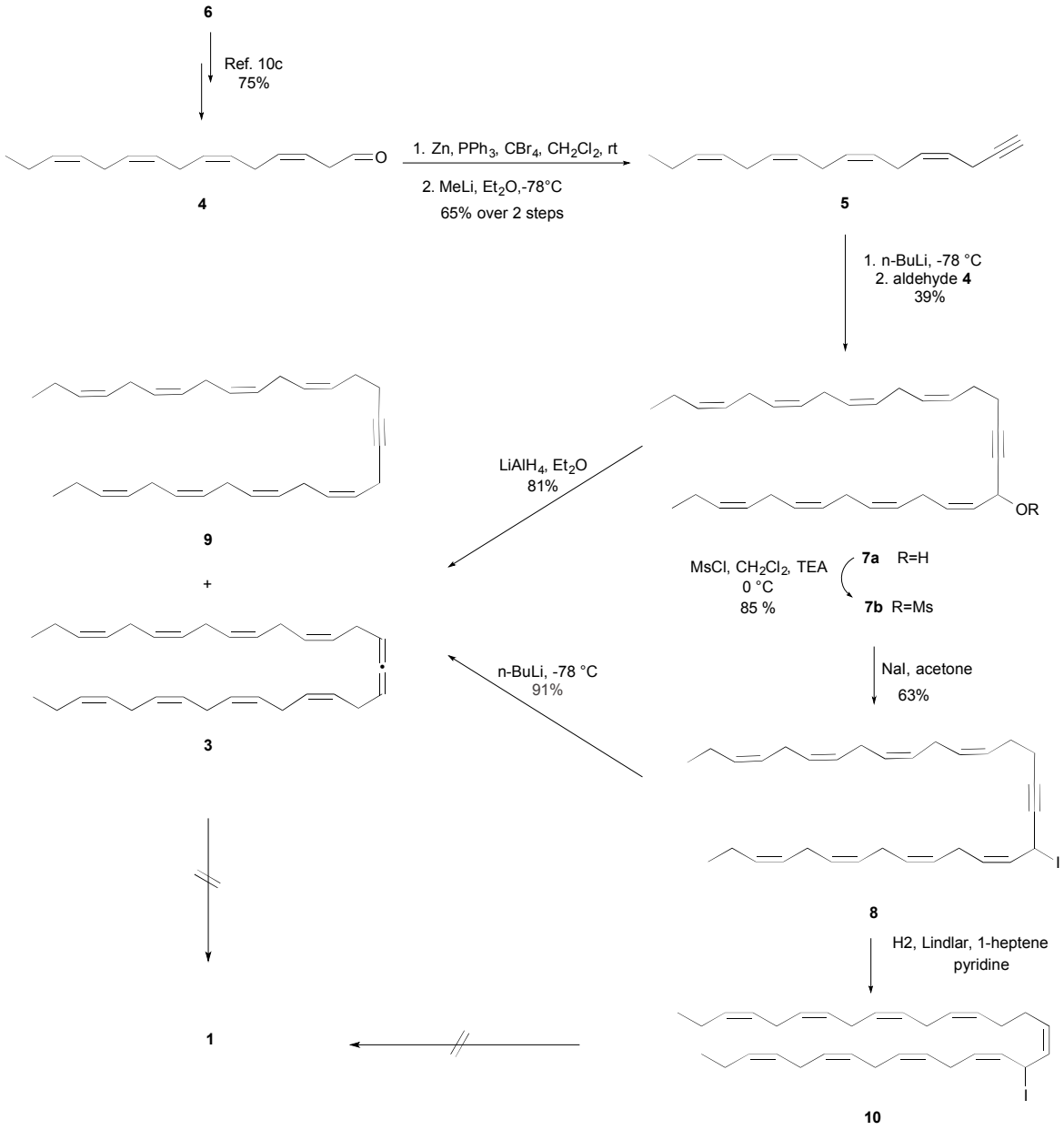



**Scheme 2** Retrosynthetic analysis of the natural occurring VLCH compound **1**.

The C15-aldehyde **4** and the terminal alkyne **5** should be easily available from the EPA ethyl ester **6**. This and similar esters have been employed as a convenient starting material for the synthesis of some methylene interrupted *Z*-double bond containing PUFAs[10c-e] and such derived natural products.[11] This type of approach renders the use of consecutive *Z*-selective Wittig

reactions[12] or stereoselective semireduction of internal alkynes[13] unnecessary. Such reactions gives most often low *Z*-selectivity.

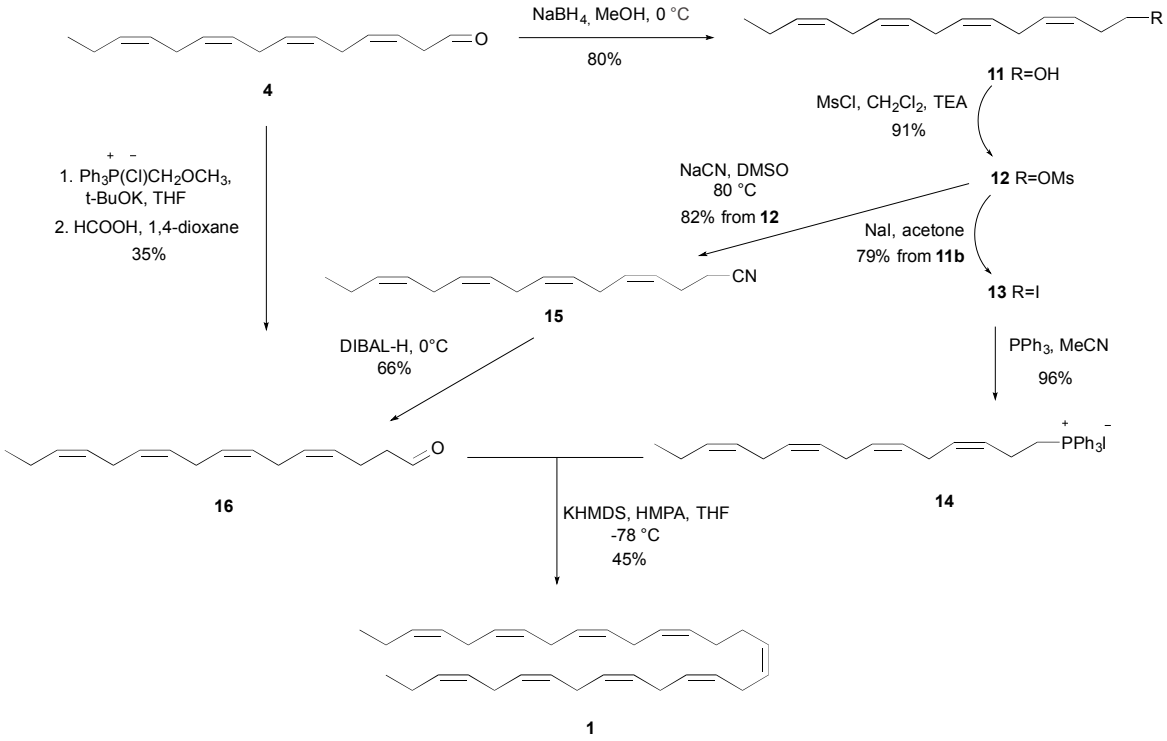
The total synthesis towards **1** commenced with the preparation of aldehyde **4** from ethyl ester **6** by an established three step procedure (Scheme 3).[10c] The aldehyde **4** was subsequently converted into the terminal C-16 alkyne **5** in 65% yield using the Corey-Fuchs reaction.[14] The treatment of alkyne **5** with *n*-BuLi at -78 °C in THF, followed by the addition of aldehyde **4**, afforded the secondary propargylic alcohol **7a** in 39% yield. Alcohol **7a** was converted into its corresponding mesylate **7b**. The subsequent reduction of the mesylate **7b** with $LiAlH_4$ led to the formation of a mixture of the desired allene **3** and the isomeric C-31 alkyne **9** in 85% yield with the allene **3** as main product. The ratio of **3** versus the other products present was 92:8 as determined by GC-analysis. Unfortunately, all efforts to obtain sufficient pure material by column chromatography, or improving the yield of **3**, failed. Then we investigated the radical deoxygenation reaction of mesylate **7b** employing a Barton-McCombie reaction[15] ($Bu_3SnH$, AIBN, dry benzene and reflux). However, only unreacted starting material **7b** was isolated. Therefore, the mesylate **7b** was converted into the propargylic iodide **8** in 63% yield by a Finkelstein reaction. The reduction of iodide **8** using a modified Lindlar hydrogenolysis protocol, using1-heptene and pyridine as additives, was then attempted.[16] The reaction afforded the vinylic C-31 iodide **10** as the main product in 55% yield after purification by column chromatography. Then compound **10** was treated with either magnesium metal or *n*-BuLi. An aqueous work-up should in either case give the target hydrocarbon **1**. However, only starting material was observed by NMR analyses. On the other hand, treatment of the propargylic iodide **8** with *n*-BuLi at -78 °C provided the generation of allene **3** that was gratifyingly isolated in an excellent 91% yield.[17] The presence of the allene functionality was confirmed by $^{13}$C-NMR (203.2 and 89.5 ppm), Raman (1955 $cm^{-1}$) and HRMS (m/z = 416.3434) experiments. Then the *Z*-selective reduction of the allenic double bond in **3** was attempted. Disappointingly, all of our attempts were unsuccessful. For example, the use of the modified Lindlar procedure, previously reported to be effective for the partial reduction of other allenes,[16] returned only the starting material **3**. When 10% Pd/C was used as catalyst for the hydrogenation reaction,[18] significant amounts of several over-reduced products were detected by NMR analyses.




**Scheme 3** Attempted synthesis of **1**.

Since the semi-reduction of the allene functionality in **3** was difficult to achieve, we turned our attention to the development of an alternative synthesis of **1**. The middle chain double bond can be constructed *via* a *Z*-selective Wittig reaction between the C-15 Wittig salt **14** and the C-16 aldehyde **16**. Noteworthy, both fragments can be obtained from aldehyde **4**. First the phosphonium iodide **14** was prepared from the C-15 aldehyde **4** in 55% yield in a four steps protocol (Scheme 4). The C-16 aldehyde **16** can be synthesized by a one-carbon elongation reaction from the same aldehyde **4**. The Wittig reaction between **4** and the ylide obtained from (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide, was followed by the consequent acid hydrolysis of the enol ether functionality in the Wittig product.[10c] This yielded aldehyde **16** in a disappointing 35% yield. Alternatively, a selective reduction of the cyanide **15**[19] should also produce aldehyde **16**. Towards these ends, the alcohol **11** was first

obtained from **4** ($NaBH_4$ in MeOH) and then converted into the mesylate **12** using standard conditions. A successful conversion of **12** by an $S_N2$-reaction (KCN, DMSO) to **15** was achieved. The DIBAL-H reduction of nitrile **15** afforded aldehyde **16** in 39% yield from aldehyde **4**. This protocol afforded the best overall yield of **16** since the Wittig reaction of the labile aldehyde **4** afforded variable amounts of isomerized products that proved difficult to separate from the desired aldehyde **16**.




**Scheme 4** The synthesis of the VLCH **1**.

Finally, the reaction between aldehyde **16** and the ylide of phosphonium iodide **14**, the latter obtained after reaction with NaHMDS in dry THF at -78 °C in the presence of HMPA, completed the total synthesis of the natural product **1**. The chemical purity and the *Z*:*E*-ratio of synthetic **1** were determined to be >95% and >98:2, respectively, by GC- and NMR-analyses. The spectral data (NMR and IR) were in agreement with literature.[5-7] Within the detection limits of $^{13}C$ NMR, no characteristic signals for allylic carbons of *E,Z*-conjugated polyolefins were observed.[20] This renders support that no isomerization of the polyene system has occurred.

## Conclusions

In summary, the first total synthesis of the natural occurring VLCH compound (all-*Z*)-hentriaconta-3,6,9,12,15,19,22,25,28-nonaene (**1**), has been achieved in eight steps and in 15% overall yield from the ethyl ester **6**. Our synthesis confirmed the structure of **1**. An advantage in the reported approach is the utilization of the same starting material for the construction of two rather similar intermediates. The developed strategy is scalable and can be used for the preparation of labeled analogs of **1** for biological studies. Of notice, the all-Z methylene interrupted double bonds remained intact throughout the synthesis of **1**. This is an advantage when employing PUFAs, such as **6**, as starting materials in total synthesis of polyunsaturated

natural products.

## EXPERIMENTAL SECTION

**General.** All reactions were performed under a nitrogen atmosphere protected from light exposure. All reagents and solvents were commercial grade and used without further purification unless when necessary. EPA ethyl ester (**6**) was obtained as a gift from Pronova Biopharma, AS, Sandefjord, Norway. Acetone was dried under anhydrous $CaSO_4$ and distilled. Thin layer chromatography (TLC) was performed using aluminum-backed silica gel 60 $F_{254}$ plates and flash chromatography utilized silica gel 60 (40-63 μm) from Merck. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded on a Bruker Ascend$^{TM}$ 400 instrument with $CDCl_3$ as a solvent. Chemical shifts are measured in ppm relative to residual solvent peak as internal standard set to δ 7.26 and 77.0. Mass spectra were recorded at 70 eV on Waters Prospec Q spectrometer using CI as the ionization method. The GC analyses were performed on Agilent GC system using an Agilent J1W HP-5 GC column (20 m, i.d. = 0.18 mm) with FID detector. IR spectra (4000 – 600 $cm^{-1}$) were recorded on a Perkin-Elmer Spectrum BX series FT-IR spectrophotometer using a reflectance cell (HATR).

**(3*Z*,6*Z*,9*Z*,12*Z*)-Pentadeca-3,6,9,12-tetraenyl methanesulfonate 12.** Mesyl chloride (1.55 mL, 20 mmol) was added to an ice-cooled solution of the alcohol **11** (2.20 g, 10 mmol) and triethylamine (2.78 mL, 20 mmol) in dry dichloromethane (30 mL). The reaction mixture was allowed to reach the room temperature and left stirring for 2 h. Brine (20 mL) was added and volatiles were removed under reduced pressure. The solution was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×15 mL), brine (2×10 mL) and dried ($Na_2SO_4$). The extract was concentrated by evaporation and the residue was purified by column chromatography eluting with hexane: EtOAc 10:1 to obtain mesylate **12** (2.72 g, 91%) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.61 - 5.23 (m, 8H), 4.20 (t, *J* = 6.8 Hz, 2H), 2.98 (s, 3H), 2.86 - 2.75 (m, 6H), 2.52 (qd, *J* = 6.9, 1.5 Hz, 2H), 2.11 - 2.01 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 132.1, 131.9, 128.7, 127.6, 127.4, 126.9, 123.3, 69.0, 37.5, 27.3, 25.7, 25.6, 25.5, 20.5, 14.3. IR: 3012, 2963, 2935, 2875, 1653, 1351, 1171, 717 $cm^{-1}$.

**(3*Z*,6*Z*,9*Z*,12*Z*)-1-Iodopentadeca-3,6,9,12-tetraene 13.** A solution of mesylate **12** (1.0 g, 3.35 mmol) and NaI (1.50 g, 10.0 mmol) in dry acetone (12 mL) was heated under reflux for 2 h. Water (50 mL) was added to the reaction mixture followed by cooling down to room temperature when ethyl ether (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2×20 mL). The combined organic extracts were washed with water, brine and dried ($MgSO_4$). Evaporation followed by silica gel column chromatography eluting with hexane gave of iodide **13** (880 mg, 79%) as a pale yellow oil. TLC (hexane, $KMnO_4$ stain): $R_f$ = 0.25. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.61 - 5.24 (m, 8H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.89 - 2.75 (m, 6H), 2.65 (qd, *J* = 7.3, 1.4 Hz, 2H), 2.06 (pd, *J* = 7.5, 1.4 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 132.1, 130.4, 128.6, 128.5, 128.3, 127.7, 127.6, 127.0, 31.5, 25.8, 25.7, 25.6, 20.6, 14.3, 5.2. IR: 3011, 2962, 2931, 2783, 1650, 1427, 1392, 1240, 1168, 713 $cm^{-1}$.

**((3*Z*,6*Z*,9*Z*,12*Z*)-Pentadeca-3,6,9,12-tetraenyl) triphenylphosphonium iodide 14.** Iodide **13** (860 mg, 2.6 mmol) was dissolved in dry acetonitrile (25 mL). Triphenylphosphine (1.73 g, 6.6

mmol) was added and then the solution was stirred under reflux for 20 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography eluting with $CH_2Cl_2$ (until all triphenylphosphine was washed out of column) followed by $CH_2Cl_2$:MeOH 95:5 to produce **14** (1.48 g, 96%) as a deep yellow syrup. The compound decomposes during storage under inert atmosphere at low temperature. TLC ($CH_2Cl_2$: MeOH 95:5, UV): $R_f$ = 0.25. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.74 (m, 9H), 7.71-7.66 (m, 6H), 5.65-5.58 (m, 1H), 5.44 - 5.12 (m, 5H), 3.87 - 3.75 (m, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.46 (dq, *J* = 16.7, 7.2 Hz, 2H), 2.02 (pd, *J* = 7.4, 1.5 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.2 (d, $^4J_{CP}$ = 3.2 Hz, 3C), 133.8 (d, $^3J_{CP}$ = 10.1 Hz, 6C), 132.2, 130.6 (d, $^2J_{CP}$ = 12.1 Hz, 6C), 130.4, 128.8 (d, $^2J_{CP}$ = 7.1 Hz), 127.5, 127.2, 126.8, 126.5 118.1 (d, $^1J_{CP}$ = 85.9 Hz, 3C), 25.6, 25.6, 25.5, 23.3 (d, $^1J_{CP}$ = 48.5 Hz), 20.6, 20.4 (d, $^3J_{CP}$ = 3 Hz), 14.3.

**(4*Z*,7*Z*,10*Z*,13*Z*)-Hexadeca-4,7,10,13-tetraenenitrile 15.** A mixture of mesylate **12** (894 mg, 3.0 mmol) and KCN (293 mg, 4.5 mmol) in DMSO (8 mL) was stirred at 70 °C for 2.5 hours. Water (30 mL) was added and the mixture was extracted with ethyl acetate (3×15 mL). The organic phases were combined; washed with brine, dried ($Na_2SO_4$) and evaporated. The crude residue was purified by column chromatography eluting with hexane: EtOAc 15:1 to obtain nitrile **14** (563 mg, 82%) as a pale yellow oil. TLC (hexane: EtOAc 15:1, $KMnO_4$ stain): $R_f$ = 0.19. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.61 -5.23 (m, 8H), 2.81 (dq, *J* = 13.0, 6.5 Hz, 6H), 2.48 - 2.30 (m, 4H), 2.06 (p, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 132.1, 131.5, 128.8, 128.7, 127.6, 127.3, 126.9, 125.5, 119.3, 25.6, 25.6, 25.5, 23.3, 20.6, 17.5, 14.3. IR: 3012, 2963, 2932, 2874, 2245, 1653, 1427, 1394, 1068, 711 cm$^{-1}$.

**(4*Z*,7*Z*,10*Z*,13*Z*)-Hexadecatetraenal 16.** *Method 1.* At 0 °C 1.0 M DIBAL-H in hexane (1.9 mL, 1.9 mmol) was added slowly to a solution of nitrile **15** (387 mg, 1.69 mmol) in 2 mL of dry ethyl ether. After 30 min the reaction was quenched with 1.0 M $H_2SO_4$ (5 mL). The salts were filtered off, brine was added and the reaction mixture was extracted with hexane. The extract was washed with brine twice, dried ($MgSO_4$) and concentrated. The residue was purified on silica gel column eluting with hexane: EtOAc 95:5 to obtain aldehyde **16** (259 mg, 66% yield) as a colourless oil.
*Method II.* The aldehyde **16** was obtained by a Wittig reaction according to the procedure reported by Langseter.[10c] $^1$H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.5 Hz, 1H), 5.46 - 5.23 (m, 8H), 2.89 - 2.72 (m, 6H), 2.49 (tt, *J* = 7.2, 1.3 Hz, 2H), 2.46 -2.32 (m, 2H), 2.06 (pd, *J* = 7.5, 1.3 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.9, 132.1, 129.4, 128.6, 128.4, 127.8, 127.8, 127.7, 127.0, 43.7, 25.6, 25.6, 25.6, 20.6, 20.1, 14.3.

**(3*Z*,6*Z*,9*Z*,12*Z*,15*Z*,19*Z*,22*Z*,25*Z*,28*Z*)-Hentriaconta-3,6,9,12,15,19,22,25,28-nonaene 1.** To the Wittig salt **14** (284 mg, 0.48 mmol) dissolved in THF (4 mL) was added molecular sieves and HMPA (0.65 mL) and the solution was cooled to -78 °C. NaHMDS (1.0 M in THF, 0.48 mL, 1.0 equiv.) was added slowly and the mixture was left stirring for 1 hour at the same temperature. Then the aldehyde **16** (93 mg, 0.4 mmol) was added at -78 °C. After the complete addition, the reaction mixture was allowed to reach ambient temperature slowly and left stirring for next 24 hours. The reaction mixture was quenched by adding phosphate buffer (pH = 7.2, 5 mL) and additional hexane (8 mL) was added. The phases were separated and the aqueous phase was extracted with hexane (8 mL) twice. The combine organic layers were washed with brine,

dried ($Na_2SO_4$) and evaporated to obtain the crude product. Purification by column chromatography eluting with hexane afforded the title compound **1** (75 mg, 45% yield) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.44 - 5.24 (m, 18H), 2.88 - 2.73 (m, 14H), 2.16 - 2.00 (m, 8H), 0.95 (t, $J$ = 7.5 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 132.02, 132.01, 129.52, 129.49, 128.54, 128.51, 128.38, 128.31, 128.22, 128.20, 128.19, 128.13, 128.06, 128.00, 127.92, 127.88, 127.02, 127.01, 27.28 (x2), 25.70 (x2), 25.65, 25.63 (x2), 25.55 (x2), 20.57 (x2), 14.28 (x2). IR: 3012, 2963, 2932, 2874, 1652, 1454, 1392, 1266, 707 cm$^{-1}$. TOF-HRMS: Exact mass calculated for $C_{31}H_{46}Na$ $[M + Na]^+$: 441.3497, found 441.3485.

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