

The syntheses of three highly unsaturated marine lipid hydrocarbons

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Starting from (all-*Z*)-icosa-5,8,11,14,17-pentaenoic acid (EPA), syntheses of the naturally occurring hydrocarbons (all-*Z*)-heneicosa-1,6,9,12,15,18-hexaene (**1**), (all-*Z*)-pentadeca-3,6,9,12-tetraen-1-yne (**2**, laurencenyne) and the corresponding 3*E*-isomer **3** (*trans*-laurencenyne) have been accomplished.

Introduction

In 1971 Halsall and Hills isolated, among other products, the highly unsaturated hydrocarbon (all-*Z*)-heneicosa-1,6,9,12,15,18-hexaene (**1**) from the brown alga *Fucus vesiculosus* L.¹ It appears to be a quite common constituent of brown algae,² probably as a metabolite of polyunsaturated fatty acids. The products from the aerial oxidation of **1** have been reported to exhibit seaweed-like, olfactory properties, a perfumery fragrance that is highly appreciated.³ From the red alga, *Laurencia okamurai*, the hydrocarbons (all-*Z*)-pentadeca-3,6,9,12-tetraen-1-yne (**2**, laurencenyne) and the corresponding 3*E*-isomer **3** (*trans*-laurencenyne) have been isolated by Yamada and co-workers.⁴ The polyene **1** has apparently not been synthesized, but syntheses of the tetraenyne **2** and **3** have been reported.⁴ As part of an ongoing study of the chemistry and biological activity of compounds derived from *n* - 3 polyunsaturated fatty acids, we have synthesized compounds **1**, **2** and **3** starting from compound **4**, the ethyl ester of icosapentaenoic acid (EPA) (Fig. 1).

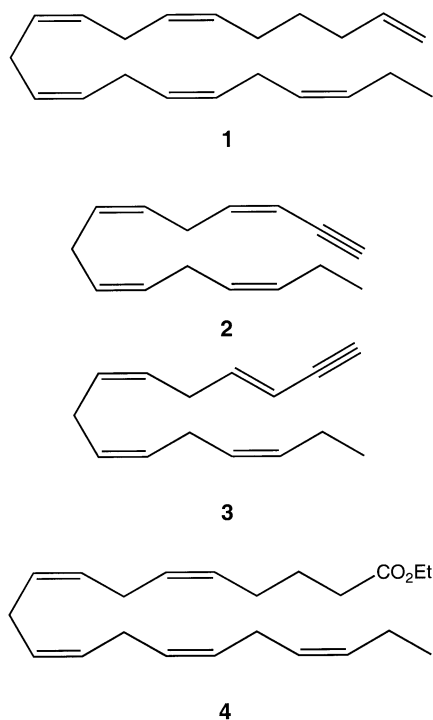
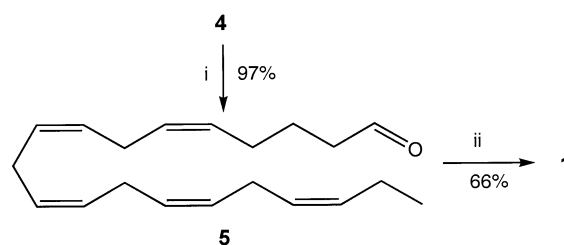


Fig. 1

Results and discussion

The synthetic route to the hexaene **1** is outlined in Scheme 1. It

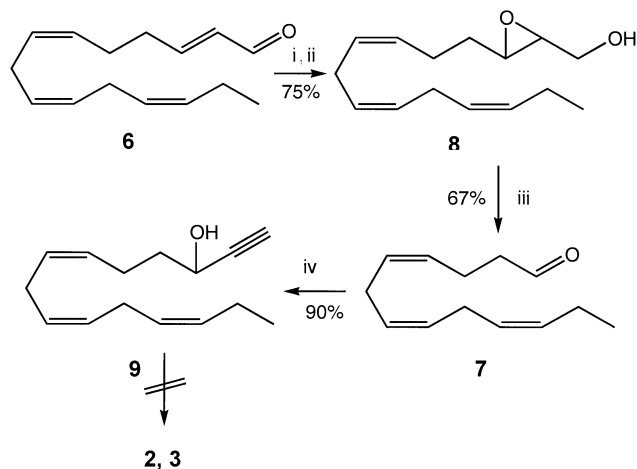


Scheme 1 Reagents and conditions: i) DIBAL-H, toluene, $-78\text{ }^{\circ}\text{C}$; ii) $\text{Ph}_3\text{P}=\text{CH}_2$.

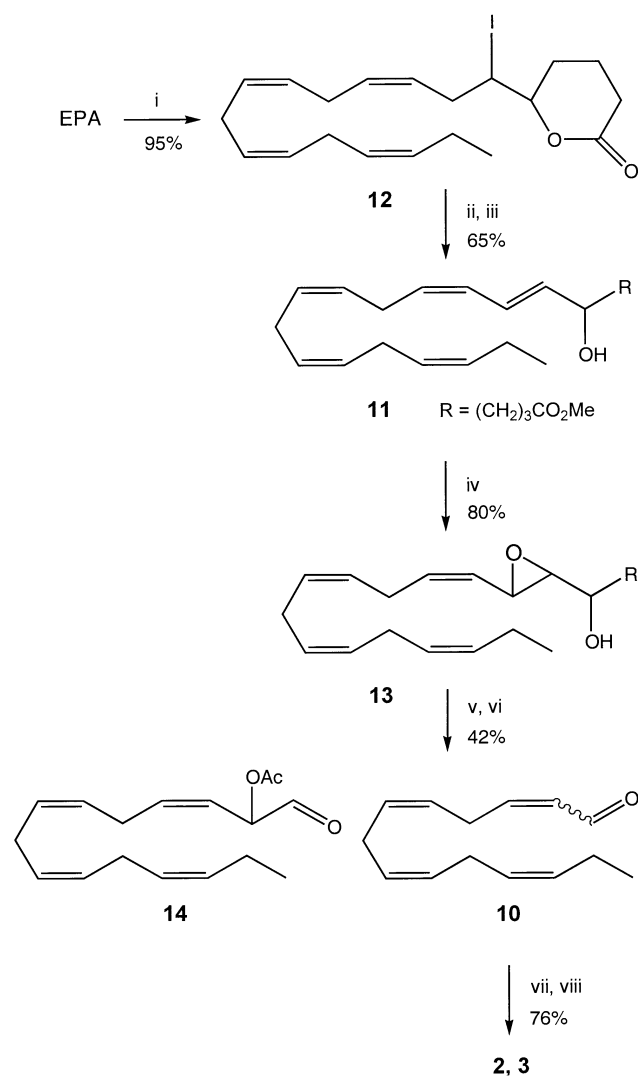
is similar to that used by Broekhof *et al.*³ for the preparation of an analogous hydrocarbon. Reduction of the ethyl ester of EPA (**4**) with diisobutylaluminium hydride at $-78\text{ }^{\circ}\text{C}$ afforded the aldehyde **5**, which reacted with methylenetriphenylphosphorane in ether to give the hexaene **1** in 64% overall yield. We did not find compound **1** to be exceptionally sensitive towards oxygen, as reported; satisfactory spectral data were obtained, including a high-resolution mass spectrum. The spectral data were in agreement with those published.³

We have previously reported⁵ the conversion of EPA into the aldehyde **6** in 75% yield by a combination of selective oxidative degradation and isomerization. We envisioned this aldehyde as a starting material for the synthesis of the isomeric acetylenic hydrocarbons **2** and **3**. Consequently, the conjugated double bond of **6** was epoxidized selectively with basic hydrogen peroxide in 89% yield. Subsequent oxidative cleavage of the epoxide ring with periodic acid in ether furnished only a low yield of the aldehyde **7**, which was not easily separated from other products. Apparently the acidic reaction conditions caused rearrangement of the epoxide prior to the oxidation. However, an alternative approach was more successful: reduction of the aldehyde to the epoxy alcohol **8** with sodium borohydride followed by periodic acid oxidation furnished pure aldehyde **7** in 56% overall yield. The aldehyde reacted with ethynylmagnesium bromide⁶ to give the alcohol **9** in 90% yield. However, all attempts to transform the alcohol by different elimination methods into the target hydrocarbons were fruitless (Scheme 2).

We then turned to the C_{14} aldehydes **10**, isomeric at the conjugated double bond, as possible precursors. The aldehydes were unknown, but we considered the hydroxy ester **11** to be a convenient starting material from which they could be



Scheme 2 Reagents and conditions: i) glycine buffer, pH 9, H_2O_2 ; ii) NaBH_4 ; iii) H_3IO_6 , ether, iv) HCCMgBr , THF, 0°C .



Scheme 3 Reagents and conditions: i) I_2 , KI, KHCO_3 ; ii) DBU; iii) MeOH, Et_3N ; iv) $t\text{-BuOOH}$, $\text{VO}(\text{acac})_2$, PhH; v) Ac_2O , DMAP, pyridine; vi) H_3IO_6 , ether; vii) CBr_4 , Ph_3P , Zn; viii) MeLi, -78°C .

prepared. The methyl ester was obtained in 65% overall yield from the readily available iodolactone **12** (Scheme 3),⁷ by a two-step procedure consisting of elimination of hydrogen iodide with DBU followed by treatment of the product with methanol. The ester was formed exclusively as the *6E*-isomer, as shown by the vicinal coupling constant of 15.2 Hz for the olefinic protons in the ^1H NMR spectrum. The ester **11** is also a naturally

occurring compound having recently been isolated from the red alga *Rhodomenia pertusa*.⁸ Selective epoxidation of the allylic double bond with *tert*-butyl hydroperoxide, catalyzed with vanadyl acetylacetonate,⁹ provided the epoxide **13** as a mixture of diastereomers in 80% yield. Several experiments designed for converting the epoxide into the aldehyde **10** were unsuccessful; the aldehydes were part of the reaction products in most cases, but separation from the other compounds present was troublesome. Finally, we found that by first protecting the hydroxy group as the acetate the periodic acid oxidation furnished the aldehyde **10** in 46% yield, easily separated from the other products by column chromatography on silica gel. It was obtained as a mixture of the *2Z*- and *2E*-isomers in a 3 : 2 ratio, respectively. We were unable to separate the stereoisomers; however, in one experiment where the reaction mixture was concentrated before extraction with hexane, only the *E*-isomer was formed. It was then possible to obtain the NMR spectrum of the *Z*-isomer from that of the mixture by subtraction. Considering the acidic reaction conditions it is not unexpected that partial isomerization of the double bond at the 2-position would occur in the oxidation step. Several minor products were formed as well, but only (all-*Z*)-2-acetoxypentadeca-3,6,9,12-tetraenal (**14**) was obtained pure in 10% yield and characterized on the basis of spectral data. The formation of **14** is probably a result of an acid catalyzed rearrangement of the epoxide **13** prior to oxidation.¹⁰ The formyl group of **10** was transformed into an ethynyl group using the Corey and Fuchs procedure;¹¹ the mixture of aldehydes was converted to the corresponding 1,1-dibromoethenyl derivatives, which by treatment with methyl lithium at -78°C afforded the tetraenynes **2** and **3** in 76% overall yield, as a 3 : 2 ratio according to GC analysis. The isomers were separated by column chromatography on silica gel, and the spectral data were in good agreement with those published;⁴ both stereoisomers exhibited IR absorption at 3280 and 2100 cm^{-1} characteristic of the ethynyl group. In the ^1H NMR spectra the vicinal coupling constant for the protons of the conjugated double bond was 10.7 and 15.9 Hz for the *Z*- and *E*-isomers, respectively.

In conclusion, we have transformed the *n* - 3 polyunsaturated acid EPA, which is widely and abundantly present in marine organisms, into some naturally occurring marine lipid hydrocarbons. The major part of the EPA molecule has been maintained unchanged during the chemical alterations.

Experimental

The NMR spectra were recorded in CDCl_3 , with a Bruker Avance DPX 200 or a Bruker Avance DPX 300 instrument. *J* values are given in Hz. The IR spectra were obtained with a Perkin-Elmer 1310 infrared spectrophotometer or a Nicolet Magna-IR 550 spectrometer. Mass spectra were recorded at 70 eV with a Fisons VG Pro spectrometer. All reactions were performed under a nitrogen or argon atmosphere.

(all-*Z*)-Icosa-5,8,11,14,17-pentaenal (**5**)

Diisobutylaluminium hydride (1 M in hexane, 3.0 ml, 3.0 mmol) was added to a solution of ethyl (all-*Z*)-icosa-5,8,11,14,17-pentaenoate (**4**) (1.0 g, 3.0 mmol) in toluene (50 ml) at -78°C . The solution was stirred at this temperature for 2 h before the addition of 1 M HCl (6 ml). The reaction mixture was warmed to room temperature and the product extracted with hexane. The combined organic layers were washed with brine, water and dried (MgSO_4). Evaporation of the solvents under reduced pressure gave the aldehyde **5** (0.83 g, 97%), sufficiently pure for further reaction. ν_{max} (film)/ cm^{-1} 3005, 2950, 1730, 1450, 1395; δ_{H} (200 MHz) 0.94 (3 H, t, *J* 7.5, CH_3), 1.68 (2 H, m, H-3), 2.08 (4 H, m, H-4, H-19), 2.41 (2 H, dt, $J_{(2,3)}$ 7.3, $J_{(2,1)}$ 1.6, H-2), 2.7–2.9 (8 H, m, $4 \times \text{CH}_2$), 5.2–5.5 (10 H, m, $10 \times \text{HC}=\text{C}$), 9.74 (1 H, t, $J_{(1,2)}$ 1.6, CHO); δ_{C} (50 MHz)

14.18 (CH₃), 20.47, 21.84, 25.45, 26.39, 43.17 (5 × CH₂), 25.54 (3 × CH₂), 126.92, 127.76, 127.95, 128.00, 128.10, 128.17, 128.47, 128.73, 128.95, 131.92 (10 × CH=), 202.23 (CHO).

(all-Z)-Henicosa-1,6,9,12,15,18-hexaene (1)

Methyltriphenylphosphonium bromide (1.1 g, 3.0 mmol) was added to a stirred solution of butyllithium (1.2 M in hexane, 2.5 ml, 3.0 mmol) in dry ether (20 ml) at room temperature. The aldehyde **5** (0.76 g, 2.7 mmol) in dry ether (10 ml) was added to the ylide solution. After 30 min water was added, and the product extracted with ether. Purification by flash chromatography (SiO₂, hexane) gave the polyene **1** (0.51 g, 66%). ν_{\max} (film)/cm⁻¹ 3010, 2940, 1640, 1440; δ_{H} (300 MHz) 0.95 (3 H, t, *J* 7.5, CH₃), 1.44 (2 H, m, H-4), 2.05 (6 H, m, H-3, H-5, H-20), 2.7–2.9 (8 H, m, 4 × CH₂), 4.9–5.1 (2 H, m, H-1), 5.2–5.5 (10 H, m, 10 × HC=), 5.8–5.9 (1 H, m, H-2); δ_{C} (75 MHz) 14.21 (CH₃), 20.51, 25.50, 25.61, 26.62, 28.80, 33.27 (6 × CH₂), 25.59 (2 × CH₂), 114.47 (C-1), 126.98, 127.90, 127.93, 128.10, 128.13, 128.36, 128.39, 128.48, 129.87, 131.93 (10 × HC=), 138.62 (C-2); *m/z* (EI) 284 (M⁺, 5%), 255, 119, 91, 79 (100) (HRMS: found M⁺ 284.2506. C₂₁H₃₂ requires 284.2504).

(all-Z)-2,3-Epoxy-pentadeca-6,9,12-trienol (8)

To a solution of aldehyde **6** (1.04 g, 4.8 mmol) in MeOH (80 ml) a glycine buffer solution of pH 9 (76 ml) and 35% H₂O₂ (1.99 g, 20.5 mmol) were added. After 6 h at room temperature water was added. The phases were separated, and the aqueous phase was extracted with hexane–ether (2 : 1). The extract was washed with brine, water and dried (MgSO₄). Filtration and evaporation of solvents gave the epoxy aldehyde (0.99 g, 89%) as a pale yellow liquid which was used further without purification. ν_{\max} (film)/cm⁻¹ 2990, 2945, 2710, 1719, 1640; δ_{H} (300 MHz) 0.94 (3 H, t, *J* 7.5, CH₃), 1.7–1.8 (2 H, m, CH₂), 2.05 (2 H, m, H-14), 2.2–2.3 (2 H, m, CH₂), 2.7–2.8 (4 H, m, 2 × CH₂), 3.12 (1 H, dd, *J*_(2,3) 2.0, *J*_(2,1) 6.2, H-2), 3.22 (1 H, dt, *J*_(3,2) 2.0, *J*_(3,4) 5.5, H-3), 5.2–5.5 (6 H, m, 6 × HC=), 8.97 (1 H, d, *J* 6.2, CHO); δ_{C} (50 MHz) 14.25 (CH₃), 20.55, 23.53, 31.14 (3 × CH₂), 25.53 (2 × CH₂), 56.26 (C-3), 59.16 (C-2), 126.89, 127.54, 127.73, 128.75, 129.61, 132.12 (6 × CH=), 198.25 (CHO); *m/z* (EI) 234 (M⁺, 3%), 148, 131, 119, 79 (100).

An ice-cooled solution of the epoxy aldehyde (0.92 g, 3.9 mmol) in MeOH (50 ml) was treated with a solution of NaBH₄ (0.52 g, 13.8 mmol) in MeOH (20 ml). The mixture was stirred for 10 min at ambient temperature after which 0.5 M HCl (60 ml) was added, and the mixture was extracted with hexane–ether (2 : 1). The extract was washed with brine, water and dried (MgSO₄). Filtration and concentration under reduced pressure gave the epoxy alcohol **8** (0.78 g, 84%) as a liquid. ν_{\max} (film)/cm⁻¹ 3424, 3015, 2964, 2933, 1652; δ_{H} (300 MHz) 0.94 (3 H, t, *J* 7.5, CH₃), 1.6–1.7 (2 H, m, CH₂), 2.04 (2 H, m, H-14), 2.2–2.3 (3 H, m, CH₂, OH), 2.7–2.9 (4 H, m, 2 × CH₂), 2.9–3.0 (2 H, m, CH₂), 3.5–3.6 (1 H, m, H-3), 3.8–3.9 (1 H, m, H-2), 5.2–5.5 (6 H, m, 6 × HC=); δ_{C} (75 MHz) 14.21 (CH₃), 20.47, 23.63, 25.44, 25.47, 31.45 (5 × CH₂), 55.43 (C-3), 58.55 (C-2), 61.61 (C-1), 126.88, 127.70, 128.47, 128.50, 128.84, 131.97 (6 × CH=); *m/z* (EI) 236 (M⁺, 0.1%), 148, 131, 119, 79 (100).

(all-Z)-Trideca-4,7,10-trienal (7)

The epoxy alcohol **8** (1.10 g, 4.7 mmol) in dry ether (25 ml) was added to a stirred mixture of periodic acid (1.51 g, 6.6 mmol) in dry ether (45 ml) at room temperature. The mixture was stirred for 3 h at this temperature, filtered and the filtrate washed with water until neutral. The extract was dried (MgSO₄), and the solvent evaporated under reduced pressure. Purification of the residue by MPLC (SiO₂, hexane–EtOAc 99 : 1) afforded the aldehyde **7** (0.60 g, 67%) as a liquid. ν_{\max} (film)/cm⁻¹ 3012, 2964, 2720, 1727, 1692, 1637; δ_{H} (200 MHz) 0.93 (3 H, t, *J* 7.5, CH₃), 2.05 (2 H, m, H-12), 2.3–2.5 (4 H, m, 2 × CH₂), 2.7–2.9 (4 H, m, 2 × CH₂), 5.2–5.5 (6 H, m, 6 × HC=), 9.73 (1 H, t, *J* 1.5, CHO);

δ_{C} (50 MHz) 14.13 (CH₃), 19.94, 20.44, 25.42, 25.45, 43.55 (5 × CH₂), 126.81, 128.58, 129.35, 131.93 (4 × CH=), 127.50 (2 × CH=), 201.72 (CHO); *m/z* (EI) 192 (M⁺, 0.6%), 148, 131, 119, 79 (100) (HRMS: found M⁺ 192.1517. C₁₃H₂₀O requires 192.1514).

(all-Z)-3-Hydroxypentadeca-6,9,12-trien-1-yne (9)

To a solution of ethynylmagnesium bromide,⁶ prepared from magnesium (0.23 g, 9.5 mmol), bromoethane and acetylene in dry THF (20 ml) and kept at 0 °C, the aldehyde **7** (0.74 g, 3.8 mmol) in dry THF (5 ml) was added dropwise. The mixture was stirred overnight at room temperature and then poured onto an ice-cooled saturated aqueous NH₄Cl solution. The phases were separated and the aqueous phase extracted with hexane–ether (2 : 1). The combined organic phases were washed with brine, water and dried (MgSO₄). Evaporation of solvents at reduced pressure afforded the alcohol **9** (0.76 g, 90%) as a pale yellow liquid. ν_{\max} (film)/cm⁻¹ 3384, 3303, 3011, 2963, 1652; δ_{H} (300 MHz) 0.95 (3 H, t, *J* 7.5, CH₃), 1.7–1.9 (2 H, m, CH₂), 1.87 (1 H, br s, OH), 2.06 (2 H, m, H-14), 2.2–2.3 (2 H, m, CH₂), 2.46 (1 H, d, *J* 2.1, H-1), 2.7–2.9 (4 H, m, 2 × CH₂), 4.3–4.4 (1 H, m, H-3), 5.2–5.5 (6 H, m, 6 × HC=); δ_{C} (75 MHz) 14.24 (CH₃), 20.53, 22.89, 25.52, 25.59, 37.31 (5 × CH₂), 61.79 (C-2), 73.09 (CH), 84.71 (C-2), 127.02, 127.91, 129.16, 132.03 (4 × CH=), 128.54 (2 × CH=); *m/z* (CI) 218 (M⁺, 4%), 147, 131, 119, 108 (100).

Methyl (6E,8Z,11Z,14Z,17Z)-5-hydroxycosa-6,8,11,14,17-pentaenoate (11)

The iodolactone **12**⁷ (5.0 g, 11.7 mmol) was dissolved in toluene (200 ml) and a solution of DBU (1.80 g, 11.8 mmol) in toluene (50 ml) was added dropwise with stirring at room temperature. After 16 h the reaction mixture was filtered and the organic solution evaporated under reduced pressure giving the pentaenyl lactone in essentially quantitative yield, and sufficiently pure for the next step. ν_{\max} (film)/cm⁻¹ 3012, 2962, 1736, 1237; δ_{H} (200 MHz) 0.92 (3 H, t, *J* 7.5, CH₃), 1.6–2.2 (6 H, m, H-3, H-4, H-19), 2.3–2.7 (2 H, m, H-2), 2.7–2.9 (4 H, m, H-13, H-16), 2.91 (2 H, m, H-10), 4.82 (1 H, m, H-5), 5.2–5.5 (7 H, m, 7 × HC=), 5.63 (1 H, dd, *J*_(6,7) 15.2, *J*_(6,5) 6.2, H-6), 5.95 (1 H, br t, *J* 11.0, H-8), 6.56 (1 H, dd, *J*_(7,6) 15.2, *J*_(7,8) 11.0, H-7); δ_{C} (50 MHz) 14.13 (CH₃), 18.14, 20.40, 25.39, 25.49, 25.97, 28.22, 29.38 (7 × CH₂), 80.43 (C-5), 126.82, 127.10, 127.12, 127.28, 127.54, 128.51, 128.71, 130.57, 131.74, 131.88 (10 × CH=), 170.91 (CO); *m/z* (EI) 300 (M⁺, 7%), 220, 91 (100) (HRMS: found M⁺ 300.2088. C₂₀H₂₈O₂ requires 300.2089).

The crude pentaenyl lactone was dissolved in MeOH (50 ml) containing Et₃N (7.0 g). After 30 min the solution was evaporated under reduced pressure, and the residue purified by chromatography (SiO₂, hexane–EtOAc 8 : 2) to give the liquid ester **11** (2.55 g, 65%); λ_{\max} (EtOH)/nm 237 (ϵ /mol⁻¹ dm³ cm⁻¹ 26400); ν_{\max} (film)/cm⁻¹ 3440, 3012, 2962, 1739, 1436; δ_{H} (300 MHz) 0.94 (3 H, t, *J* 7.5, CH₃), 1.5–1.9 (4 H, m, H-3, H-4), 1.89 (1 H, br s, OH), 2.04 (2 H, m, H-19), 2.31 (2 H, t, *J* 7.2, H-2), 2.7–2.9 (4 H, m, 2 × CH₂), 2.93 (2 H, m, CH₂), 3.63 (3 H, s, OCH₃), 4.13 (1 H, m, H-5), 5.2–5.5 (7 H, m, 7 × HC=), 5.64 (1 H, dd, *J*_(6,7) 15.2, *J*_(6,5) 6.7, H-6), 5.95 (1 H, br t, *J* 11.0, H-8), 6.49 (1 H, dd, *J*_(7,6) 15.2, *J*_(7,8) 11.0, H-7); δ_{C} (75 MHz) 14.18 (CH₃), 20.47, 20.74, 25.47, 25.57, 26.01 (5 × CH₂), 33.71 (C-2), 36.49 (C-4), 51.46 (OCH₃), 72.16 (C-5), 128.57 (2 × CH=), 125.53, 126.91, 127.46, 127.68, 127.88, 130.35, 132.00, 135.98 (8 × CH=), 173.93 (CO); *m/z* (EI) 332 (M⁺, 0.6%), 234, 206, 91 (100) (HRMS: found M⁺ 332.2370. C₂₁H₃₂O₃ requires 332.2351).

Methyl (all-Z)-5-hydroxy-6,7-epoxycosa-8,11,14,17-tetraenoate (13)

To a solution of the ester **11** (1.5 g, 4.5 mmol) and vanadyl

acetylacetonate (212 mg, 0.8 mmol) in dry benzene (80 ml) was added *tert*-butyl hydroperoxide (1.4 ml, 7.7 mmol). After 2 h at ambient temperature a solution of Na₂SO₃ (1.2 g) in water (20 ml) was added at 0 °C. The mixture was stirred for 20 min at room temperature and then extracted with ether. The extract was washed with brine and dried (MgSO₄). Evaporation of the solvents followed by flash chromatography (SiO₂, CH₂Cl₂-ether 9 : 1, 1% Et₃N) gave the epoxy alcohol **13** (1.25 g, 80%) as the diastereomers **A** and **B**.

Diastereomer A. ν_{\max} (film)/cm⁻¹ 3467, 3013, 2963, 1739, 1437; δ_{H} (200 MHz) 0.94 (3 H, t, *J* 7.5, CH₃), 1.4–1.9 (4 H, m, H-3, H-4), 2.04 (3 H, m, H-19, OH), 2.34 (2 H, t, *J* 7.1, H-2), 2.70–2.85 (4 H, m, H-13, H-16), 2.85–2.90 (1 H, m, H-6), 2.90–3.0 (2 H, m, H-10), 3.5–3.6 (2 H, m, H-7, H-5), 3.64 (3 H, s, OCH₃), 5.07 (1 H, ddt, *J*_(8,7) 9.0, *J*_(8,9) 10.9, *J*_(8,10) 1.5, H-8), 5.2–5.5 (6 H, m, 6 × HC=), 5.68 (1 H, dt, *J*_(9,8) 10.9, *J*_(9,10) 7.6, H-9); δ_{C} (50 MHz) 14.20 (CH₃), 20.50, 20.70, 25.48, 25.57, 26.02, 33.68, 33.77 (C-2), 51.53 (OCH₃), 52.07 (C-7), 62.61 (C-6), 70.26 (C-5), 126.18, 126.85, 127.00, 127.48, 128.75, 129.11, 132.06, 135.06 (8 × HC=), 173.78 (CO); *m/z* (EI) 348 (M⁺, 0.17%), 147, 131, 99 (100) (HRMS: found M⁺ 348.2285. C₂₁H₃₂O₄ requires 348.2301).

Diastereomer B. ν_{\max} (film)/cm⁻¹ 3467, 3013, 2963, 1739, 1437; δ_{H} (200 MHz) 0.92 (3 H, t, *J* 7.5, CH₃), 1.4–1.9 (4 H, m, H-3, H-4), 2.02 (2 H, m, H-19), 2.30 (1 H, br s, OH), 2.32 (2 H, t, *J* 7.1, H-2), 2.70–2.85 (4 H, m, H-13, H-16), 2.85–2.90 (1 H, m, H-6), 2.90–3.0 (2 H, m, H-10), 3.61 (3 H, s, OCH₃), 3.67 (1 H, dd, *J*_(7,8) 9.0, *J*_(7,6) 2.2, H-7), 3.75–3.82 (1 H, m, H-5), 5.06 (1 H, ddt, *J*_(8,7) 9.0, *J*_(8,9) 10.9, *J*_(8,10) 1.5, H-8), 5.2–5.5 (6 H, m, 6 × HC=), 5.65 (1 H, dtd, *J*_(9,8) 10.9, *J*_(9,10) 7.6, *J*_(9,7) 0.7, H-9); δ_{C} (50 MHz) 14.14 (CH₃), 20.43, 20.61, 25.41, 25.51, 25.95, 32.55 (6 × CH₂), 33.64 (C-2), 50.44 (C-7), 51.44 (OCH₃), 61.96 (C-6), 67.99 (C-5), 126.32, 126.81, 126.97, 127.44, 128.67, 129.01, 131.96, 134.84 (8 × HC=), 173.80 (CO); *m/z* (EI) 348 (M⁺, 0.07%), 147, 131, 99 (100) (HRMS: found M⁺ 348.2306. C₂₁H₃₂O₄ requires 348.2301).

(2*E*1*Z*,5*Z*,8*Z*,11*Z*)-Tetradeca-2,5,8,11-tetraenal (**10**)

To a solution of the epoxy alcohol **13** (0.76 g, 2.2 mmol) in CH₂Cl₂ (20 ml) was added pyridine (420 μ l, 5.2 mmol), acetic anhydride (230 μ l, 2.4 mmol) and DMAP (25 mg, 0.2 mmol). The mixture was stirred for 2 h at room temperature. Hexane was added and the organic layer was washed twice with saturated aqueous NH₄Cl, water and dried (MgSO₄). Evaporation of the solvents gave the epoxy acetate (0.79 g, 92%) as a mixture of diastereomers. ν_{\max} (film)/cm⁻¹ 3013, 2963, 1740, 1235; δ_{H} (300 MHz) 0.92 (3 H, t, *J* 7.5, CH₃), 1.6–1.8 (4 H, m, H-3, H-4), 1.9–2.1 (2 H, m, H-19), 2.01 (3 H, s, C(O)CH₃), 2.25–2.35 (2 H, m, H-2), 2.7–3.0 (7 H, m, H-6, H-10, H-13, H-16), 3.45–3.60 (1 H, m, H-6), 3.61 (3 H, s, OCH₃), 4.6–4.8 (1 H, m, H-5), 4.95–5.05 (1 H, m, H-8), 5.2–5.5 (6 H, m, 6 × HC=), 5.6–5.7 (1 H, m, H-9); δ_{C} (75 MHz) 14.13 (CH₃), 20.26, 20.43, 20.79, 20.85, 25.41, 25.49, 25.93, 25.96, 30.59, 33.44, 51.42, 52.02, 52.95, 59.35, 60.05, 72.19, 72.78, 125.93, 126.11, 126.77, 126.83, 126.88, 126.95, 127.36, 127.48, 128.65, 128.73, 129.00, 129.08, 131.94, 131.98, 134.90, 135.17, 170.07, 170.14, 173.22, 173.35; *m/z* (EI) 390 (M⁺, 0.6%), 131, 79, 43 (100) (HRMS: found M⁺ 390.2410. C₂₃H₃₄O₅ requires 390.2406).

A solution of the epoxy acetate (1.1 g, 2.8 mmol) in dry ether (5 ml) was added to a stirred mixture of periodic acid (0.77 g, 3.4 mmol) in dry ether (25 ml) at room temperature. The mixture was further stirred for 30 min at this temperature. Hexane was added and the organic layer was washed with saturated aqueous NaHCO₃, water and dried (MgSO₄). Evaporation of the solvents under reduced pressure and purification of the residue by flash chromatography under argon (SiO₂, hexane-EtOAc) afforded the liquid aldehyde **10** (266 mg, 46%), as a 3 : 2

mixture of 2*Z*- and 2*E*-isomers, which we were unable to separate. In addition, the acetoxyaldehyde **14** (80 mg, 10%) was obtained as a liquid.

2*E*-Isomer. ν_{\max} (film)/cm⁻¹ 3013, 2964, 2725, 1694, 1127; δ_{H} (200 MHz) 0.92 (3 H, t, *J* 7.5, CH₃), 2.02 (2 H, m, H-13), 2.7–2.9 (4 H, m, H-7, H-10), 3.07 (2 H, m, H-4), 5.2–5.6 (6 H, m, 6 × HC=), 6.10 (1 H, ddt, *J*_(2,3) 15.6, *J*_(2,1) 7.8, *J*_(2,4) 1.6, H-2), 6.79 (1 H, dt, *J*_(3,2) 15.6, *J*_(3,4) 6.2, H-3), 9.48 (1 H, d, *J*_(1,2) 7.8, CHO); δ_{C} (50 MHz) 14.14 (CH₃), 20.47, 25.43, 25.51, 30.39 (4 × CH₂), 123.70, 126.66, 126.97, 128.94, 131.31, 132.04, 132.89, 156.07 (8 × HC=), 193.68 (CHO).

2*Z*-Isomer. δ_{H} (200 MHz) 0.94 (3 H, t, *J* 7.5, CH₃), 2.03 (2 H, m, H-13), 2.7–2.9 (4 H, m, H-7, H-10), 3.35 (2 H, m, H-4), 5.2–5.6 (6 H, m, 6 × HC=), 5.94 (1 H, ddt, *J*_(2,3) 11.1, *J*_(2,1) 7.8, *J*_(2,4) 1.6, H-2), 6.53 (1 H, dt, *J*_(3,2) 11.1, *J*_(3,4) 8.0, H-3), 10.08 (1 H, d, *J*_(1,2) 7.8, CHO); δ_{C} (50 MHz) 14.21 (CH₃), 20.54, 25.53, 25.64, 26.43 (4 × CH₂), 124.98, 126.68, 126.99, 129.13, 129.71, 130.71, 132.20, 150.32 (8 × HC=), 190.63 (CHO).

Mixture of isomers: *m/z* (EI) 204 (M⁺, 28%), 186, 129, 91 (100) (HRMS: found M⁺ 204.1515. C₁₄H₂₀O requires 204.1514).

(all-*Z*)-2-Acetoxy-pentadeca-3,6,9,12-tetraenal (14**).** ν_{\max} (film)/cm⁻¹ 3018, 2964, 2720, 1740, 1226; δ_{H} (200 MHz) 0.95 (3 H, t, *J* 7.5, CH₃), 2.05 (2 H, m, H-14), 2.16 (3 H, s, COCH₃), 2.7–2.9 (4 H, m, 2 × CH₂), 2.98 (2 H, m, CH₂), 5.2–5.5 (7 H, m, 7 × HC=), 5.81 (1 H, br d, *J* 8.3, H-2), 5.8–5.9 (1 H, m, HC=), 9.43 (1 H, s, CHO); δ_{C} (50 MHz) 14.22 (CH₃), 20.57 (CH₃), 20.52, 25.51, 25.62, 26.73 (4 × CH₂), 75.46 (C-2), 119.34, 126.12, 126.83, 127.31, 128.91, 129.74, 132.10, 137.26 (8 × HC=), 170.00, 194.30 (CHO).

Laurencenyne **2** and **3**

A mixture of triphenylphosphine (806 mg, 3.1 mmol), zinc (200 mg, 3.1 mmol) and tetrabromomethane (1.02 g, 3.1 mmol) in CH₂Cl₂ (15 ml) was stirred at room temperature for 20 h before a solution of freshly prepared aldehyde **10** (230 mg, 1.13 mmol) in CH₂Cl₂ (5 ml) was added. The mixture was stirred for 2 h at room temperature. Evaporation of the solvent at reduced pressure and filtration through a plug of SiO₂ with hexane gave the dibromide (386 mg, 95%) as a mixture of the *Z*- and *E*-isomers. A solution of the crude dibromide (360 mg, 1.0 mmol) in dry ether was cooled to –78 °C before addition of methylolithium (1.6 M in ether, 1.0 ml, 1.6 mmol). The mixture was stirred overnight at –70 °C. A saturated aqueous solution of NH₄Cl and hexane was added. The organic layer was separated, washed with water and dried (MgSO₄). Filtration through a plug of SiO₂ and evaporation of the solvents under reduced pressure gave laurencenyne **2** and **3** (160 mg, 80%) in a 3 : 2 ratio. The stereoisomers were separated by flash chromatography under argon (SiO₂, hexane). The spectral data were in agreement with those of the literature.⁴ ν_{\max} (film)/cm⁻¹ 3280, 2990, 2100, 1680, 1650.

Laurencenyne (2). *R_f* 0.17 (hexane); δ_{H} (300 MHz) 0.96 (3 H, t, *J* 7.5, CH₃), 2.06 (2 H, m, H-14), 2.7–2.9 (4 H, m, H-8, H-11), 3.0–3.2 (3 H, m, H-1, H-5), 5.2–5.6 (7 H, m, 7 × HC=), 5.93 (1 H, dtd, *J* 10.7, *J* 7.4, *J* 0.7, H-4); δ_{C} (75 MHz) 14.25 (CH₃), 20.54, 25.54, 25.71, 28.70 (4 × CH₂), 80.19 (C-2), 81.79 (C-1), 108.29, 126.01, 127.01, 127.71, 128.66, 129.59, 132.04, 143.53 (8 × CH=); *m/z* (EI) 199 (M⁺ – 1, 5.5%), 91 (100) (HRMS: found M⁺ – 1 199.1478. C₁₅H₄₉ requires 199.1487).

trans-Laurencenyne (3). *R_f* 0.13 (hexane); δ_{H} (300 MHz) 0.96 (3 H, t, *J* 7.5, CH₃), 2.06 (2 H, m, H-14), 2.7–3.0 (7 H, m, H-1, H-5, H-8, H-11), 5.2–5.6 (7 H, m, 7 × HC=), 6.22 (1 H, dt, *J* 15.9, *J* 6.4, H-4); δ_{C} (75 MHz) 14.23 (CH₃), 20.55, 30.59

(2 × CH₂), 25.53 (2 × CH₂), 76.20 (C-1), 82.34 (C-2), 108.95, 125.29, 126.90, 127.47, 128.78, 130.23, 132.09, 144.17 (8 × CH=); *m/z* (EI) 199 (M⁺ - 1, 1.9%), 91 (100) (HRMS: found M⁺ - 1 199.1491. C₁₅H₄₉ requires 199.1487).

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