

# Oxidative degradation of eicosapentaenoic acid into polyunsaturated aldehydes

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**Abstract**—Eicosapentaenoic acid is converted in good overall yield to an  $\alpha,\beta$ -ethylenic epoxide derivative. The oxidative cleavage of the epoxide ring with periodic acid in ether proceeded in part with acid-catalyzed rearrangement of the vinyl epoxide moiety prior to cleavage. Among the products were 2*E*- and 2*Z*, 5*Z*, 8*Z*, 11*Z*-tetradecatetraenal, 4-hydroxy-2*E*,6*Z*,9*Z*,12*Z*-pentadecatetraenal and (all-*Z*)-2-methoxy-3,6,9,12-pentadecatetraenal.

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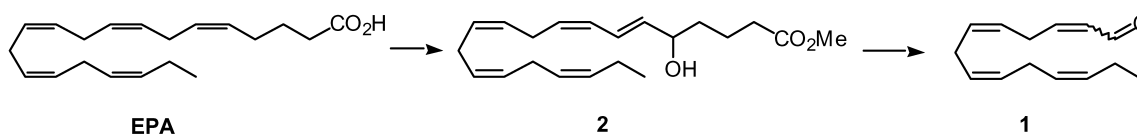
## 1. Introduction

Methylene interrupted double bonds as they are present in naturally occurring polyunsaturated fatty acids are most commonly constructed by semireduction of the corresponding acetylenic compounds or by using Wittig type reactions.<sup>1</sup> The main problem with these methods is the stereoselectivity of the double bond forming reactions. Another approach to this class of compound involves the selective degradation of abundantly available polyunsaturated fatty acids to useful starting materials for further synthesis, one of the advantages being the conservation in the final product of some of the double bonds originally present in the starting material. This ensures a regio- and stereochemically pure product, provided the chemical manipulations take place without isomerization. We have used this approach starting from the naturally occurring fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid for the successful syntheses of a variety of polyunsaturated compounds.<sup>2–5</sup> In connection with the syntheses of some naturally occurring polyunsaturated hydrocarbons we have recently reported<sup>5</sup> a protocol for the conversion of EPA into a mixture of 2*E*- and 2*Z*, 5*Z*, 8*Z*, 11*Z*-tetradecatetraenal (**1**) in 20% overall yield involving the allylic alcohol **2** as an intermediate (Scheme 1). The

present paper describes a synthetic study with aldehyde **1** as the primary target and the oxidative cleavage of an epoxide with periodic acid as the key reaction.

## 2. Results and discussion

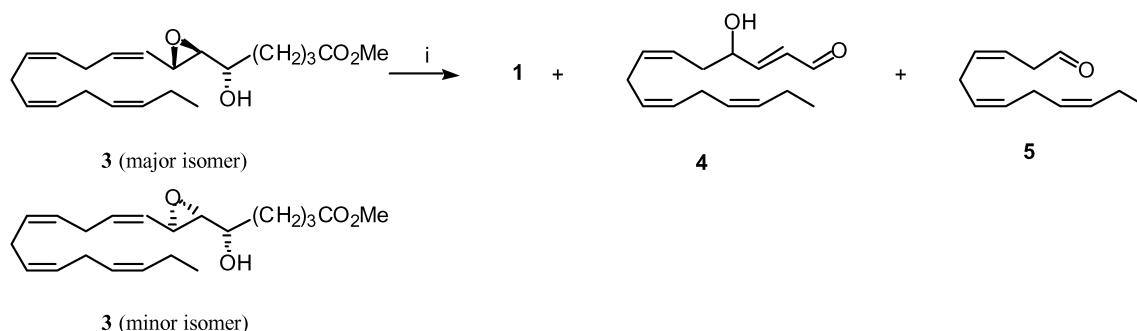
Oxidation of the allylic alcohol **2** with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate afforded a mixture of diastereomeric epoxy alcohols from which the major isomer **3** was separated by flash chromatography; the spectral data corresponds to diastereomer B in the previously published article.<sup>5</sup> The <sup>1</sup>H NMR spectrum is practically identical with that of the product obtained from the Sharpless oxidation of **2**,<sup>6</sup> in the presence of (+) diisopropyl tartrate; hence, the diastereomers of the epoxy alcohol **3** have been assigned the stereochemistry depicted in Scheme 2.<sup>7</sup> The oxidative cleavage of **3** with periodic acid<sup>5</sup> in dry ether furnished a mixture of the aldehydes **1** (36% yield), **4** (17%) and **5** (traces).<sup>8</sup> The compounds were easily separated by flash chromatography and the structural assignments are based on spectral data. The <sup>1</sup>H NMR spectrum showed by the coupling constants that **1** was formed as an approximately 1:3 mixture of the 2*Z*- and 2*E*-isomers, the ratio being



Scheme 1.

**Keywords:** polyunsaturated aldehydes; epoxides; Payne type rearrangement.

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**Scheme 2.** Reagents and conditions: (i)  $\text{H}_5\text{IO}_6$ , ether, rt.

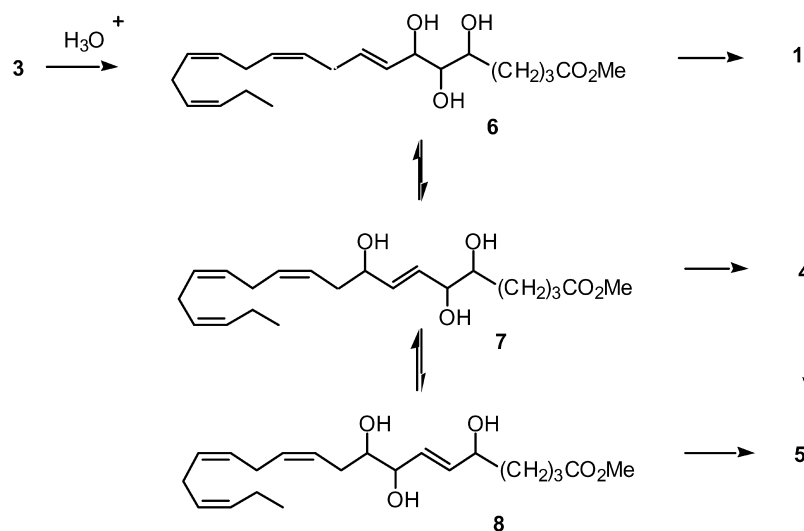
somewhat dependent on reaction time. On the other hand the aldehyde **4** is formed exclusively as the *2E*-isomer and the aldehyde **5** as the all-*Z* isomer. The formation of **4** requires the presence of water during the oxidation reaction and the only source is periodic acid, which is used as the dihydrate in stoichiometric amounts (Scheme 2).

Lead tetraacetate oxidation of a vicinal diol proceeds most probably through a cyclic intermediate, and a similar mechanism has been suggested for the oxidative cleavage of an epoxide by periodic acid.<sup>9</sup> Our results indicate that the vinyl epoxide undergoes proton catalyzed ring opening to an allylic cation, which reacts with water to give the triols **6** and **7** (Scheme 3). The triol **7** may also equilibrate under the reaction conditions to the triol **8**. Subsequent oxidative cleavage of the glycolic C–C bonds of these triols provides an explanation for the observed products. The *E*-configuration has been assigned to the double bond adjacent to the hydroxyl group for each of the triols; support for the assignment has been obtained by the isolation of a monomethylated derivative of the triol **7**, for which an *E*-configuration of this double bond has been established (vide infra). The triol **8** is probably not the only precursor to the aldehyde **5**; a separate experiment revealed that the  $\alpha,\beta$ -unsaturated aldehyde **4** is converted slowly to **5** under the reaction conditions, probably initiated by an acid catalyzed Michael addition of water. Moreover, it is reasonable to

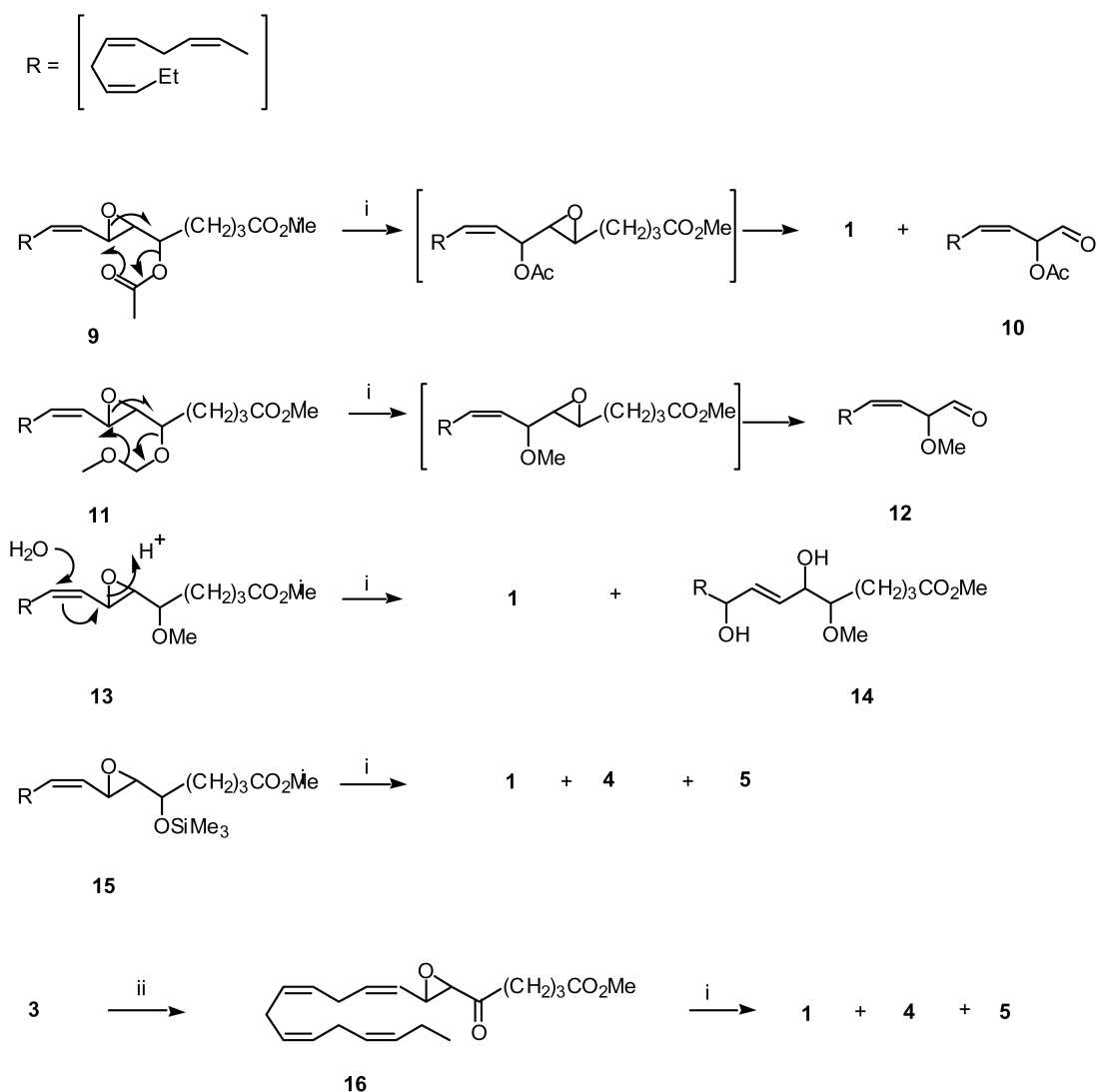
assume that at least some of aldehyde **1** is formed directly from the epoxide. Falck *et al.*<sup>10</sup> has reported the acid catalyzed ring opening of an  $\alpha,\beta$ -unsaturated epoxide with a result similar to ours.

Aiming at a procedure with improved selectivity and yield of the desired aldehyde, the hydroxyl group of **3** was protected. As already reported<sup>5</sup> oxidation of the acetate **9** with periodic acid in ether furnished the aldehyde **1** as a mixture of the *2E* and *2Z* isomers in 46% yield, the best yield of this compound obtained so far. In addition, the 2-acetoxy aldehyde **10** was isolated in 10% yield. Variations in the amount of periodic acid used as well as the reaction temperature did not alter significantly the product composition. The formation of **10** is particularly interesting. Apparently, periodic acid catalyzes epoxide migration prior to the oxidative ring cleavage, although we cannot exclude that the species actually being oxidized is the corresponding vicinal diol. A similar reaction with the MOM protected compound **11** led to the 2-methoxy derivative **12** as the only aldehyde in 42% yield. A rearrangement similar to that suggested for the acetate **9** can explain this result as well. A proposed mechanism for this Payne type rearrangement is depicted in Scheme 4.

This type of epoxide migration<sup>11</sup> usually takes place under basic conditions, but examples of acid catalyzed



**Scheme 3.**

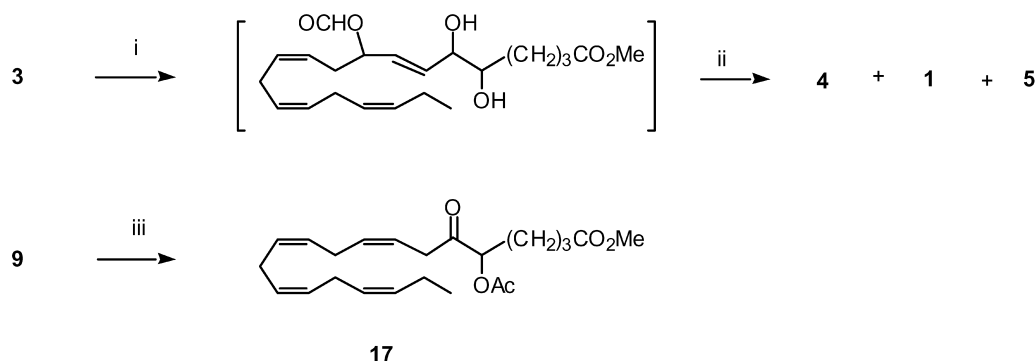


**Scheme 4.** Reagents and conditions: (i)  $\text{H}_5\text{IO}_6$ , ether, rt; (ii) periodinane,  $\text{CH}_2\text{Cl}_2$ , rt.

rearrangement have been reported.<sup>12,13</sup> We anticipated that the reaction of the methoxy derivative **13** with periodic acid would occur without migration, and the product consisted of the aldehyde **1** (29%) in addition to 49% of an inseparable diastereomeric mixture of the diol **14**; the *7E* configuration of **14** was assigned based on a coupling constant of 15.6 Hz for the pertinent olefinic protons. Formation of the diol is explained by addition of water concurrent with double bond migration and ring opening of the epoxide, as outlined in Scheme 4. Being a mono methylated derivative of the triol **7**, the presence of the diol **14** supports the proposed reaction path to the 4-hydroxy aldehyde **4** (Scheme 3). We could not detect any of this hydroxy aldehyde in the reaction mixture, indicating that at least under our reaction conditions the diol **14** is not cleaved by periodic acid. Furthermore, oxidation of the trimethylsilyl protected derivative **15** furnished a mixture of the hydroxy aldehyde **4** (45%) and the aldehydes **1** (39%) and **5** (traces). It seems unlikely that the silyl ether is hydrolyzed to **3** prior to oxidation, since the product from the same reaction of **3** contained none of the aldehyde **5**, and the aldehydes **1** and **4** were formed in quite a different ratio as well. Finally, Dess–Martin oxidation of **3** provided the

epoxy ketone **16** in high yield, but its oxidation by periodic acid led only to a disappointingly low yield of aldehyde **1** (26%), admixed with aldehydes **4** (4%) and **5** (traces).

With regard to the yield of aldehyde **1**, protection of the hydroxyl function led only to a minor improvement. One problem seemed to be the presence of water in the reaction mixture, supplied by the periodic acid reagent. Hence, we deliberately opened the epoxide **3** with formic acid–acetic anhydride and oxidized the product with sodium metaperiodate. This reaction sequence furnished the aldehyde **4** in 40% overall yield, in addition to small amounts of aldehydes **1** and **5**. Due to the anhydrous conditions of this reaction the formate anion must be the nucleophile in the ring opening of the epoxide and the formate ester formed is probably hydrolyzed to **4** during the work-up procedure. By the same protocol the methoxy derivative **13** afforded, besides traces of aldehyde **1**, a diastereomeric mixture of the diol **14** in 55% yield. We also tried to trap as the acetonide the vicinal diol that might result from the aluminum chloride catalysed ring opening of the epoxide **9**; however, the reaction conditions favored rearrangement of the epoxide to the



**Scheme 5.** Reagents and conditions: (i) HCO<sub>2</sub>H, Ac<sub>2</sub>O rt; (ii) H<sub>5</sub>IO<sub>6</sub>, ether, rt; (iii) AlCl<sub>3</sub>, ether, rt.

ketone **17**, which was isolated as the only product in 76% yield (Scheme 5).

### 3. Conclusion

In conclusion, the synthetic effort so far has only provided the aldehyde **1** in moderate yield. The aldehyde has already served as starting material for the syntheses of laurencenyne and *trans*-laurencenyne, two naturally occurring hydrocarbons from a red alga.<sup>5</sup> However, the aldehydes **4** and **10** are actually quite interesting as they may serve as starting material for the syntheses of lipoxygenase derived EPA metabolites. Further studies along this line are in progress.

## 4. Experimental

### 4.1. General

The NMR spectra were recorded in CDCl<sub>3</sub>, with a Bruker Avance DPX 200 instrument or a Bruker Avance DPX 300 instrument. 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 nitrogen or argon atmosphere.

**4.1.1. Methyl (all-*Z*)-5-methoxymethylenoxy-6,7-epoxy-8,11,14,17-eicosatetraenoate (11).** To the epoxide **3**<sup>5</sup> (major diastereomer; 1.0 g, 2.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added *N*-ethyl-diisopropylamine (995 μL, 5.8 mmol) and chloromethyl methyl ether (330 μL, 4.35 mmol) at 0°C. The mixture was stirred for 48 h at rt, diluted with hexane and washed with saturated aqueous NH<sub>4</sub>Cl solution, water and dried (MgSO<sub>4</sub>). Evaporation of solvents and purification of the residue by flash chromatography (SiO<sub>2</sub>, 9:1 CH<sub>2</sub>Cl<sub>2</sub>/ether) gave the epoxide **11** (720 mg, 63%) as an oil.  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2990, 2935, 1730;  $\delta_{\text{H}}$  (300 MHz) 0.94 (t, *J*=7.5 Hz, 3H, CH<sub>3</sub>), 1.5–1.9 (m, 4H, H-3, H-4), 2.04 (m, 2H, H-19), 2.32 (m, 2H, H-2), 2.7–3.1 (m, 7H, H-6, H-10, H-13, H-16), 3.31 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.3–3.5 (m, 1H, H-5), 3.59 (dd, *J*=9.0, 2.0 Hz, 1H, H-7), 3.64 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.62 (dd, *J*=6.8 Hz, 2H, OCH<sub>2</sub>OCH<sub>3</sub>), 5.04 (m, 1H, H-8), 5.2–5.5 (m, 6H, 6×HC=), 5.66 (m, 1H, H-9);  $\delta_{\text{C}}$  (75 MHz) 14.21 (CH<sub>3</sub>), 20.50, 20.59, 25.48, 25.57, 25.99, 32.18 (6×CH<sub>2</sub>), 33.82 (C-2), 51.45 (CO<sub>2</sub>CH<sub>3</sub>), 53.14 (C-7), 55.45 (OCH<sub>3</sub>), 60.70 (C-6), 75.91 (C-5), 96.03 (OCH<sub>2</sub>OCH<sub>3</sub>),

126.62, 126.90, 127.14, 127.58, 128.69, 129.02, 132.02, 134.76 (8×CH=), 173.70 (CO<sub>2</sub>CH<sub>3</sub>); *m/z* (CI, NH<sub>3</sub>) 410 ([M+18]<sup>+</sup>, 5), 343, 331, 175 (100%).

**4.1.2. Methyl (all-*Z*)-5-methoxy-6,7-epoxy-8,11,14,17-eicosatetraenoate (13).** Epoxide **3** (major diastereomer; 840 mg, 2.4 mmol) and iodomethane (1.1 mL, 17.4 mmol) in DMF (6 mL) was added to a stirred slurry of NaH (104 mg, 4.4 mmol) in dry DMF (2 mL) at 0°C. The mixture was warmed to rt and stirred at this temperature over night. A saturated aqueous NH<sub>4</sub>Cl solution was added and the product was extracted with ether. The organic phase was washed with water and dried (MgSO<sub>4</sub>). Evaporation of solvents and purification of the residue by flash chromatography (SiO<sub>2</sub>, 8:2 hexane/EtOAc) gave the epoxide **13** (470 mg, 54%) as an oil.  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2990, 2940, 1725;  $\delta_{\text{H}}$  (300 MHz) 0.94 (t, *J*=7.5 Hz, 3H, CH<sub>3</sub>), 1.5–1.9 (m, 4H, H-3, H-4), 2.05 (m, 2H, H-19), 2.32 (t, *J*=7.2 Hz, 2H, H-2), 2.7–3.1 (m, 8H, H-5, H-6, H-10, H-13, H-16), 3.36 (s, 3H, OCH<sub>3</sub>), 3.60 (dd, *J*=9.0, 1.7 Hz, 1H, H-7), 3.64 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 5.06 (m, 1H, H-8), 5.2–5.5 (m, 6H, 6×HC=), 5.68 (m, 1H, H-9);  $\delta_{\text{C}}$  (50 MHz) 14.22 (CH<sub>3</sub>), 20.52, 20.56, 25.50, 25.59, 26.02, 31.82, 33.90 (7×CH<sub>2</sub>), 51.47 (CO<sub>2</sub>CH<sub>3</sub>), 52.93 (CH), 58.01 (OCH<sub>3</sub>), 60.60 (CH), 79.70 (C-5), 126.63, 126.86, 127.17, 127.51, 128.75, 129.02, 132.06, 134.74 (8×CH=), 173.78 (CO<sub>2</sub>CH<sub>3</sub>).

**4.1.3. Methyl (all-*Z*)-5-trimethylsilyloxy-6,7-epoxy-8,11,14,17-eicosatetraenoate (15).** To the epoxide **3** (major diastereomer; 600 mg, 1.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added pyridine (380 μL, 4.71 mmol), trimethylchlorosilane (261 μL, 2.80 mmol) and DMAP (20 mg, 0.16 mmol). The mixture was stirred for 2 h at rt. Hexane was added and the organic layer was washed twice with saturated aqueous NH<sub>4</sub>Cl solution, water and dried (MgSO<sub>4</sub>). Evaporation of solvents and purification by flash chromatography (SiO<sub>2</sub>, 9:1 hexane/EtOAc) gave the epoxide **15** (611 mg, 84%) as an oil.  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2990, 2940, 1725, 1240;  $\delta_{\text{H}}$  (300 MHz) 0.01 (s, 9H, SiMe<sub>3</sub>), 0.92 (t, *J*=7.5 Hz, 3H, CH<sub>3</sub>), 1.4–1.8 (m, 4H, H-3, H-4), 2.02 (m, 2H, H-19), 2.29 (m, 2H, H-2), 2.7–3.1 (m, 7H, H-7, H-10, H-13, H-16), 3.4–3.6 (m, 2H, H-5, H-6), 3.61 (s, 3H, OCH<sub>3</sub>), 5.03 (m, 1H, H-8), 5.2–5.5 (m, 6H, 6×HC=), 5.62 (m, 1H, H-9);  $\delta_{\text{C}}$  (75 MHz) 0.13 (SiMe<sub>3</sub>), 14.14 (CH<sub>3</sub>), 20.44, 20.62, 25.42, 25.52, 25.96, 33.81, 34.12 (7×CH<sub>2</sub>), 51.34 (CO<sub>2</sub>CH<sub>3</sub>), 51.94, 61.99, 70.90 (3×CH), 126.76, 126.83, 127.06, 127.48, 128.64, 128.94, 131.93, 134.38 (8×CH=), 173.66 (CO<sub>2</sub>CH<sub>3</sub>); *m/z* (EI) 420 (M<sup>+</sup>, 0.7), 203

(100), 73 (52%); (HRMS (EI):  $M^+$ , found 420.2728.  $C_{24}H_{40}O_4Si$  requires 420.2696).

**4.1.4. Reaction of epoxide 2a with periodic acid. General procedure.** A solution of epoxide **3** (1.2 g, 3.4 mmol) in dry ether (7 mL) was added to periodic acid (1.5 g, 6.6 mmol) in dry ether (200 mL) at rt. The mixture was stirred for 1 h at this temperature. Hexane was added and the organic layer was washed with a saturated aqueous  $NaHCO_3$  solution, brine and dried ( $MgSO_4$ ). Evaporation of solvent under reduced pressure and purification of the residue by flash chromatography, using argon ( $SiO_2$ , 95:5  $CH_2Cl_2$ /ether) gave the aldehyde **1**<sup>5</sup> (250 mg, 36%) as a 3:1 mixture of the *E*- and *Z*-isomers, traces of aldehyde **5**<sup>8</sup> and 4-hydroxy-2*E*, 6*Z*, 9*Z*, 12*Z*-pentadecatetraenal (**4**, 17%):  $\nu_{max}$  (film)/ $cm^{-1}$  3441, 3012, 2964, 1690, 1139, 1101;  $\delta_H$  (200 MHz) 0.95 (t,  $J=7.5$  Hz, 3H,  $CH_3$ ), 1.97 (d,  $J=4.5$  Hz, 1H, *OH*), 2.04 (m, 2H, H-14), 2.43 (m, 2H, H-5), 2.7–2.9 (m, 4H, H-8, H-11), 4.46 (m, 1H, H-4), 5.2–5.6 (m, 6H,  $6\times HC=$ ), 6.32 (ddd,  $J_{2,3}=15.7$  Hz,  $J_{2,1}=7.8$  Hz,  $J=1.6$  Hz, 1H, H-2), 6.81 (dd,  $J_{3,2}=15.7$  Hz,  $J_{3,4}=4.3$  Hz, 1H, H-3), 9.57 (d,  $J_{1,2}=7.8$  Hz, 1H, *CHO*);  $\delta_C$  (50 MHz) 14.23 ( $CH_3$ ), 20.56, 25.55, 25.75, 34.52 ( $4\times CH_2$ ), 70.37 (C-4), 123.41, 126.73, 127.09, 129.08, 131.00, 132.20, 132.92, 157.75 ( $8\times CH=$ ), 193.33 (*CHO*);  $m/z$  (EI) 149 ( $[M-C_4H_5O_2]^+$ , 10), 93, 79 (100%); (HRMS, (electrospray):  $[M+1]^+$ , found 235.1685.  $C_{15}H_{23}O_2$  requires 235.1693).

**4.1.5. Reaction of epoxide 11 with periodic acid.** By the general procedure the reaction gave after flash chromatography, using argon ( $SiO_2$ , 9:1 hexane/EtOAc) traces of aldehyde **1** and (all-*Z*)-2-methoxy-3,6,9,12-pentadecatetraenal (**12**, 44%):  $\nu_{max}$  (film)/ $cm^{-1}$  3013, 2965, 2704, 1739, 1693, 1111;  $\delta_H$  (200 MHz) 0.95 (t,  $J=7.5$  Hz, 3H,  $CH_3$ ), 2.05 (m, 2H, H-14), 2.7–3.0 (m, 6H, H-3, H-8, H-11), 3.39 (s, 3H,  $OCH_3$ ), 4.45 (br d,  $J=8.4$  Hz, 1H, H-2) 5.2–5.5 (m, 7H,  $7\times HC=$ ), 5.84 (dtd,  $J=10.8$ , 7.5, 1.3 Hz, 1H, H-4), 9.51 (d,  $J=1.5$  Hz, 1H, *CHO*);  $\delta_C$  (75 MHz) 14.15 ( $CH_3$ ), 20.47, 25.46, 25.57, 26.60 ( $4\times CH_2$ ), 56.76 ( $OCH_3$ ), 82.63 (C-2), 122.32, 126.44, 126.78, 127.36, 128.75, 129.27, 132.02, 136.32 ( $8\times HC=$ ), 198.52 (*CHO*).

**4.1.6. Reaction of epoxide 13 with periodic acid.** Using the general procedure, the reaction product consisted of the aldehyde **1** (29%), as a 3:1 mixture of the *E*- and *Z*-isomers, and methyl 5-methoxy-6,9-dihydroxy-7*E*, 11*Z*, 14*Z*, 17*Z*-eicosatetraenoate (**14**, 49%), as a mixture of two diastereomers:  $\nu_{max}$  (film)/ $cm^{-1}$  3424, 3012, 2961, 1739, 1106;  $\delta_H$  (500 MHz) 0.95 (t,  $J=7.5$  Hz, 3H,  $CH_3$ ), 1.4–1.8 (m, 4H, H-3, H-4), 2.05 (m, 2H, H-19), 2.2–2.4 (m, 4H, H-2, H-10), 2.7–2.9 (m, 4H, H-13, H-16), 3.1–3.2 (m, 1H, H-5), 3.40 (s, 3H,  $OCH_3$ ), 3.64 (s, 3H,  $CO_2CH_3$ ), 4.1–4.2 (m, 1H, H-9), 4.3–4.4 (m, 1H, H-6), 5.3–5.5 (m, 5H,  $5\times HC=$ ), 5.5–5.6 (m, 1H,  $HC=$ ), 5.68 (dddd,  $J=15.6$ , 6.0, 4.3, 1.1 Hz, 1H, H-7), 5.80 (dddd,  $J=15.6$ , 6.0, 3.0, 2.0, 1.2 Hz, 1H, H-8);  $\delta_C$  (126 MHz) 14.25 ( $CH_3$ ), 20.53, 21.02, 21.14, 25.53, 25.78, 28.36, 28.42, 33.88, 33.90, 35.11, 35.13, 51.56 ( $CO_2CH_3$ ), 57.90 ( $OCH_3$ ), 57.94 ( $OCH_3$ ), 71.58 (CH), 71.67 (CH), 71.86 (CH), 71.89 (CH), 83.73 (C-5), 83.75 (C-5), 124.84, 126.92, 127.59, 127.60, 128.30, 128.72, 128.87, 128.97, 131.20, 131.24, 132.07, 134.64, 134.71, 173.99 ( $CO_2CH_3$ ), 174.00 ( $CO_2CH_3$ );  $m/z$  (CI,  $NH_3$ ) 398 ( $[M+18]^+$ , 0.2), 380 ( $M^+$ , 0.1), 345, 331, 145 (100%).

**4.1.7. Reaction of epoxide 15 with periodic acid.** By the general procedure the reaction gave the aldehyde **1** (39%) as a 7:1 mixture of the *Z*- and *E*-isomers, aldehyde **4** (45%), and traces of aldehyde **5**.

**4.1.8. Methyl (all-*Z*)-5-oxo-6,7-epoxy-8,11,14,17-eicosatetraenoate (16).** The epoxide **3** (770 mg, 2.2 mmol) was added to a stirred solution of periodinane (1.16 g, 2.7 mmol) in  $CH_2Cl_2$  (60 mL) at rt. The mixture was stirred for 1 h and then filtered through a silica plug with  $CH_2Cl_2$ . Evaporation of solvent under reduced pressure and purification of the residue by flash chromatography ( $SiO_2$ , 9:1 hexane/EtOAc) afforded the epoxy ketone **16** (700 mg, 92%) as an oil.  $\nu_{max}$  (film)/ $cm^{-1}$  3013, 2963, 1737, 1713, 1436, 1203;  $\delta_H$  (200 MHz) 0.92 (t,  $J=7.5$  Hz, 3H,  $CH_3$ ), 1.8–2.0 (m, 2H, H-3), 2.02 (m, 2H, H-19), 2.2–2.6 (m, 4H, H-2, H-4), 2.7–2.9 (m, 4H, H-13, H-16), 2.9–3.0 (m, 2H, H-10), 3.33 (d,  $J=1.9$  Hz, 1H, H-6), 3.62 (s, 3H,  $OCH_3$ ), 3.71 (ddd,  $J=8.6$ , 1.9, 0.8 Hz, 1H, H-7), 5.02 (ddt,  $J=8.7$ , 10.9, 1.6 Hz, 1H, H-8), 5.2–5.5 (m, 6H,  $6\times HC=$ ), 5.74 (dtd,  $J=10.9$ , 7.6, 0.7 Hz, 1H, H-9);  $\delta_C$  (50 MHz) 14.15 ( $CH_3$ ), 18.11, 20.45, 25.43, 25.53, 26.00 ( $5\times CH_2$ ), 32.71 (C-2), 36.31 (C-4), 51.48 ( $CO_2CH_3$ ), 53.80 (C-7), 60.52 (C-6), 124.97, 126.51, 126.74, 127.29, 128.78, 129.38, 132.02, 136.54 ( $8\times CH=$ ), 173.27 ( $CO_2CH_3$ ), 205.85 (*CO*);  $m/z$  (EI) 346 ( $M^+$ , 0.1), 210, 129 (100), 101 (94%); (HRMS (EI):  $M^+$ , found 346.2139  $C_{21}H_{30}O_4$  requires 346.2144).

**4.1.9. Reaction of epoxy ketone 16 with periodic acid.** A solution of epoxy ketone **16** (330 mg, 0.95 mmol) in dry ether (2 mL) was added to a solution periodic acid (260 mg, 1.14 mmol) in dry ether (7 mL) at rt. For completion more periodic acid (390 mg, 1.71 mmol) was added and the mixture was stirred for 4 h at rt. Hexane was added and the solution was washed with a saturated aqueous  $NaHCO_3$  solution, brine and dried ( $MgSO_4$ ). Evaporation of solvents under reduced pressure and purification of the residue by flash chromatography, using argon ( $SiO_2$ ,  $CH_2Cl_2$  to 9:1  $CH_2Cl_2$ /ether) gave the aldehyde **1** (51 mg, 26%) as the *E*-isomer, aldehyde **4** (6 mg, 4%) and traces of aldehyde **5**.

**4.1.10. Reaction of epoxide 3 with formic acid–acetic anhydride followed by sodium metaperiodate.** A solution of epoxide **3** (550 mg, 1.58 mmol) in formic acid (5 mL) and acetic anhydride (0.5 mL) was stirred at 0°C for 2 h and at rt for 1 h. Volatile compounds were evaporated under reduced pressure. Ether was added to the residue and the solution was washed with a saturated aqueous  $NaHCO_3$  solution and dried ( $MgSO_4$ ). The solvent was evaporated under reduced pressure, the residue was dissolved in MeOH (8 mL) and  $K_2CO_3$  (640 mg) was added. The reaction mixture was stirred for 1 h at rt, water was added and the product extracted with ether. The extract was washed with water and concentrated under reduced pressure. The residue was dissolved in MeOH (6 mL), cooled to 0°C and a solution of sodium metaperiodate (507 mg, 2.37 mmol) in water (2 mL) was added. The mixture was stirred for 1.5 h at 0°C and 30 min at rt, diluted with water and extracted with ether. The extract was washed with water and dried ( $MgSO_4$ ). Evaporation of solvents under reduced pressure, followed by flash chromatography ( $SiO_2$ , 7:3 hexane/EtOAc) gave the aldehyde **4** (146 mg, 40%) and traces of aldehydes **1** and **5**.



**4.1.11. Reaction of epoxide 13 with formic acid–acetic anhydride followed by sodium metaperiodate.** By the above procedure the reaction gave the diol **14** (55%) as a mixture of two diastereomers and traces of aldehyde **1**.

**4.1.12. Methyl (all-Z)-5-acetoxy-6-oxoeicosa-8,11,14,17-tetraenoate (17).** A mixture of the epoxide **9**<sup>5</sup> (1.9 g, 4.9 mmol) and AlCl<sub>3</sub> (33 mg, 0.2 mmol) in dry acetone (20 mL) was stirred at rt for 2 days. A saturated solution of NaHCO<sub>3</sub> was added and the mixture was stirred for another 30 min before extraction with ether. The organic phase was washed with water and dried (MgSO<sub>4</sub>). Evaporation of solvents under reduced pressure followed by flash chromatography (SiO<sub>2</sub>, 8:2 hexane/EtOAc) gave the ketone **17** (1.4 g, 76%) as an oil.  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3010, 2963, 1740, 1437, 1235;  $\delta_{\text{H}}$  (300 MHz) 0.92 (t,  $J=7.5$  Hz, 3H, CH<sub>3</sub>), 1.4–1.9 (m, 4H, H-3, H-4), 2.0–2.1 (m, 2H, H-19), 2.08 (s, 3H, C(O)CH<sub>3</sub>), 2.29 (t,  $J=7$  Hz, 2H, H-2), 2.6–2.9 (m, 6H, H-10, H-13, H-16), 3.1–3.2 (m, 2H, H-7), 3.61 (s, 3H, OCH<sub>3</sub>), 5.0–5.1 (m, 1H, H-5), 5.2–5.4 (m, 6H, 6×HC=), 5.5–5.6 (m, 2H, H-8, H-9);  $\delta_{\text{C}}$  (75 MHz) 14.13 (CH<sub>3</sub>), 20.42 (CH<sub>2</sub>), 20.50 (CH<sub>2</sub>, CH<sub>3</sub> overlapping signals), 25.40 (2×CH<sub>2</sub>), 29.49, 30.27, 33.17, 42.40 (4×CH<sub>2</sub>), 51.47 (CO<sub>2</sub>CH<sub>3</sub>), 77.42 (C-5), 121.19, 127.67, 128.44, 128.90, 131.88, 133.24 (6×CH=), 126.89 (2×CH=), 170.28, 173.19 (2×C=O), 205.08 (C-6);  $m/z$  (EI) 390 (M<sup>+</sup> 1.3), 174 (9.7), 131 (73), 43 (100%); (HRMS (EI): M<sup>+</sup> found 390.2388 C<sub>23</sub>H<sub>34</sub>O<sub>5</sub> requires 390.2406).

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