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Syntheses of Some Polyunsaturated Sulfur- and Oxygen-containing Fatty Acids Related to Eicosapentaenoic and Docosahexaenoic Acids

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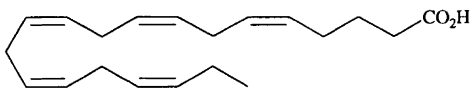
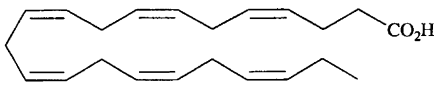
With the aim of enhancing selectively the beneficial biological effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) a number of polyunsaturated fatty acids containing sulfur or oxygen atoms in the chain has been synthesized starting from EPA and DHA, respectively. Oxidative degradation of these acids led to the corresponding aldehydes all-(*Z*)-3,6,9,12-pentadecatetraenal and all-(*Z*)-3,6,9,12,15-octadecapentaenal. Reactions with DBU converted these aldehydes quantitatively into the conjugated isomers (2*E*,6*Z*,9*Z*,12*Z*)-pentadecatetraenal and (2*E*,6*Z*,9*Z*,12*Z*,15*Z*)-octadecapentaenal, respectively. The four aldehydes were transformed by a sequence of reactions comprising reduction to the alcohols, halogenation and substitution with mercapto esters into the corresponding sulfur containing polyunsaturated fatty acid esters. The oxygen containing esters were prepared from the respective alcohol by boron trifluoride catalysed reaction with ethyl diazoacetate.

The importance of all-(*Z*)-5,8,11,14,17-eicosapentaenoic acid (EPA, **1**) and all-(*Z*)-4,7,10,13,16,19-docosahexaenoic acid (DHA, **2**) in human nutrition is universally recognized.[1] Indeed, results so far indicate that they are essential for normal growth and cell function in humans. A substantial amount of pharmacological and clinical data accumulated in recent years indicates a wide spectrum of biological effects for these $n-3$ highly unsaturated fatty acids, particularly in relation to cardiovascular and inflammatory diseases; however, an intake of fairly large amounts of the acids over an extended period of time seems necessary in order to achieve significant results.[1]

Both EPA and DHA are incorporated into cell membrane phospholipids; however, it seems documented that only the former acid is competetive with arachidonic acid as a substrate for the oxidative enzymes, e.g. cyclooxygenases and lipoxygenases, involved in the eicosanoid cascade of reactions. EPA is also converted at a considerably slower rate than arachidonic acid into the corresponding prostanoid derivatives of lower and different biological activity. It has been suggested that the beneficial medicinal effects of EPA are most likely due to this inhibitory effect.[2] The mechanism by which DHA exerts its biological activity is less well understood. This acid also seems to be a substrate for the above enzymes but little is known about the resulting metabolic products. The main metabolic pathway for fatty acids generally is through β-oxidation. Oxidations at the α- and ω-positions are important as well, but occur at a considerably slower rate. Branching at the β-position or replacing the β-methylene group with sulfur or oxygen should delay the oxidative degradation of the fatty acid. This could result in enhanced and/or prolonged biological activity of the modified EPA and DHA derivatives. We have previously prepared derivatives of EPA with methyl substitution at the α- and β-positions, and their biological effects appeared encouraging.[3] Moreover, saturated fatty acids with sulfur atoms in the chain exhibit interesting



EPA, **1**



DHA, **2**

Scheme 1.

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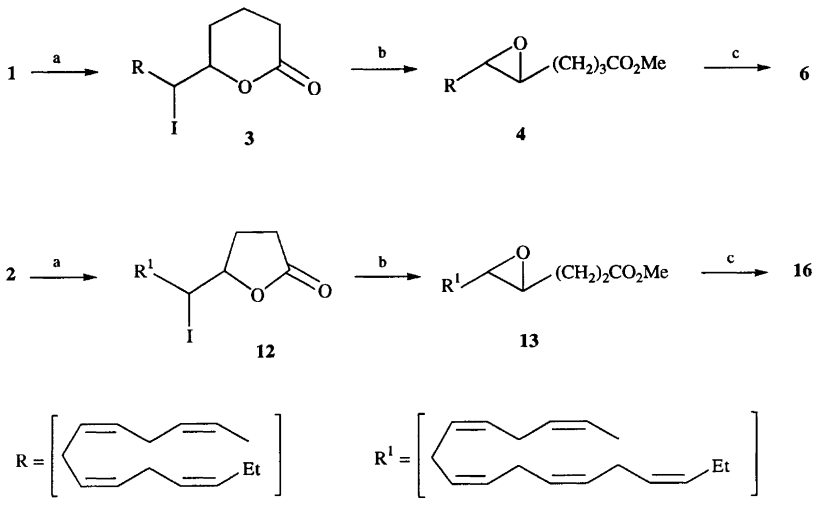
biological effects; reduced blood lipid concentration has been observed.[4] Hence, sulfur- and oxygen-containing analogues of EPA and DHA would be of interest for biological screening. In the present paper we report the syntheses of a number of such derivatives based on EPA and DHA as starting materials.

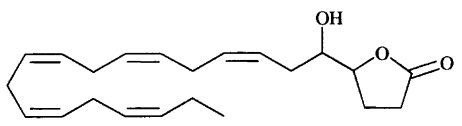
Results and discussion

Sufficiently pure ethyl esters of EPA and DHA were available in quantity and the free acids were obtained by hydrolysis with lithium hydroxide in ethanol–water at room temperature. Under these conditions no isomerization of the double bonds was detected. Corey and coworkers have shown that arachidonic acid,[5] EPA[6] and DHA[7] can be converted selectively into the corresponding iodolactones, which subsequently gave the monoepoxides with base. The reaction of EPA with iodine, potassium iodide and potassium bicarbonate at room temperature for 48 h gave the δ-iodolactone **3** which by treatment with potassium carbonate in methanol at room temperature furnished the epoxide **4** in 85% overall yield. Oxidation with periodic acid dihydrate in ether for one and a half hours at room temperature gave a complex reaction product. The unavoidable purification by column chromatography caused loss of the aldehyde **5** resulting in poor reproducibility and low isolated yields. When the periodic acid oxidation was carried out in dry methanol the corresponding acetal **6** was obtained in a 45% reproducible yield (Scheme 2); moreover, the acetal is quite stable and a convenient derivative of the aldehyde for storage. It was quantitatively hydrolysed with 80% aqueous formic acid to the aldehyde **5**. Reduction with sodium borohydride gave the corresponding alcohol **7** which was converted into the bromide **8** with bromotriphenylphosphonium bromide in acetonitrile (Scheme 3). Finally, reaction of the bromide with methyl mercaptoacetate and lithium hydroxide in methanol afforded methyl all-(*Z*)-3-thia-6,9,12,15-octadecatetraenoate (**9**). Similar reactions of **8** with methyl 3-mercaptopropionate and with γ-thiobutyrolactone afforded the corresponding esters **10a** and **11a**, respectively (Scheme 4). The yields of all these reactions were good.

The same protocol was followed for the conversion of DHA, through the iodolactone **12** into the epoxide **13** in 89% overall yield. We encountered the same problems with the periodic acid oxidation of the epoxide; a complex mixture was obtained containing the lactone **14** as a major component together with the aldehyde **15**[8] (Scheme 2). The latter has been prepared independently by Kuklev *et al.*[9] by essentially the same procedure in a similar low yield. The separation of the product mixture was troublesome and again it was advantageous to use dry methanol as the solvent, conditions that gave the acetal **16** in 46% yield after flash chromatography. By the same sequence of reactions as those reported above



Reagents: a: I_2, KI, $KHCO_3$, THF/H_2O, b: K_2CO_3, MeOH, c: H_5IO_6, dry MeOH



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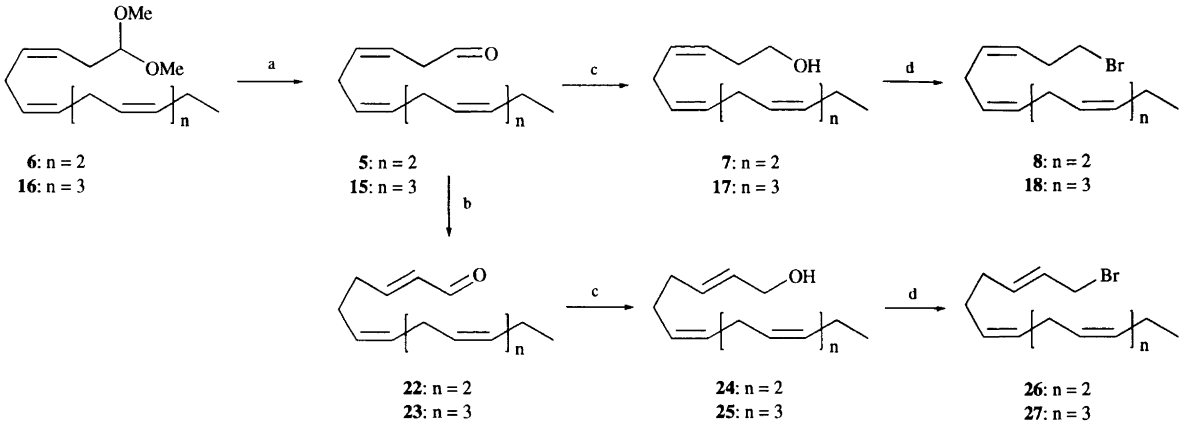
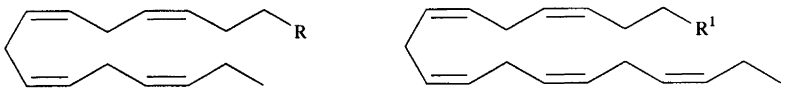
Scheme 2.



Scheme 3. Reagents: a, 80% HCO_2H, dioxane–H_2O; b, DBU, Et_2O; c, $NaBH_4$, MeOH; d, Br_2, Ph_3P, pyridine, CH_3CN.



9a: R = SCH_2CO_2Me
9b: R = SCH_2CO_2H
10a: R = $SCH_2CH_2CO_2Me$
10b: R = $SCH_2CH_2CO_2H$
11a: R = $SCH_2CH_2CH_2CO_2Me$
11b: R = $SCH_2CH_2CH_2CO_2H$
20a: R = OCH_2CO_2Et
20b: R = OCH_2CO_2H

19a: R^1 = SCH_2CO_2Me
19b: R^1 = SCH_2CO_2H
21a: R^1 = OCH_2CO_2Et
21b: R^1 = OCH_2CO_2H

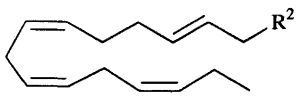
Scheme 4.

the acetal **16** was converted into the alcohol **17** and subsequently into the bromide **18** in good overall yield. (Scheme 3). The bromide was further transformed with methyl mercaptoacetate into the thiaester **19**, but reactions with other mercapto esters were not carried out because elongation of the chain beyond 21 atoms was considered unfavourable with respect to anticipated biological activity.

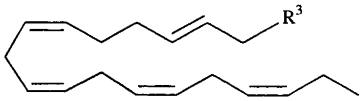
In order to prepare derivatives in which an oxygen atom is part of the chain we first resorted to a Williamson type reaction between the anion of the alcohol **7** and methyl bromoacetate. This was not successful because the basic conditions combined with the reaction temperature required for an acceptable reaction rate caused isomerization of the double bonds. However, boron trifluoride-catalysed reactions of methylene chloride solutions of the alcohols **7** and **17** with ethyl diazoacetate, furnished the oxa-esters **20a** and **21a**, respectively, in about 50% yields. These conditions gave the ethers in yields that compare well with those reported for similar ethers using rhodium acetate catalysis.[10]

While working with the aldehydes **5** and **15** we noticed that prolonged contact with either acid or base caused some isomerization; consequently treatment of the aldehydes with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for about one hour at room temperature brought about complete rearrangement of the $\Delta^{3,4}$ double bond resulting in the conjugated aldehydes **22** and **23**, which actually turned out to be considerably more stable than their precursors. The 2*E*-configuration was confirmed by ^1H NMR analysis, showing a pattern of signals characteristic of a *trans* α,β-unsaturated aldehyde with $J_{2,3} = 15.6$ Hz. Reduction with sodium borohydride afforded the corresponding allylic alcohols **24** and **25**, which were transformed into the bromides **26** and **27** with bromotriphenylphosphonium bromide in acetonitrile (Scheme 3). The bromide **26** was subsequently treated with the same sulfur reagents as those employed for the bromide **8** furnishing the sulfur-containing methyl esters **28a**–**30a** in good yields; reaction of the bromide **27** with methyl mercaptoacetate furnished the ester **31a**. Furthermore, the BF_3-catalysed reactions of the alcohols **24** and **25** with ethyl diazoacetate gave the oxa-esters **32a** and **33a**, respectively, in about 50% yields (Scheme 5).

All new compounds were characterized spectroscopically. The NMR spectra in particular provided conclusive structural evidence. Because of the highly unsaturated nature of the compounds, with methylene-interrupted double bonds, they are all prone to undergo oxidation by molecular oxygen; however, they could be stored in frozen benzene under nitrogen at −20 °C for several months without any detectable change. Furthermore, the methylene-interrupted double bonds may rearrange



28a: $R^2 = SCH_2CO_2Me$
28b: $R^2 = SCH_2CO_2H$
29a: $R^2 = SCH_2CH_2CO_2Me$
29b: $R^2 = SCH_2CH_2CO_2H$
30a: $R^2 = SCH_2CH_2CH_2CO_2Me$
30b: $R^2 = SCH_2CH_2CH_2CO_2H$
32a: $R^2 = OCH_2CO_2Et$
32b: $R^2 = OCH_2CO_2H$



31a: $R^3 = SCH_2CO_2Me$
31b: $R^3 = SCH_2CO_2H$
33a: $R^3 = OCH_2CO_2Et$
33b: $R^3 = OCH_2CO_2H$

Scheme 5.

under basic conditions to conjugated isomers, the presence of which are easily observed in the ^1H NMR spectrum; however, except for the aldehydes the experimental conditions employed caused no detectable isomerization of the double bonds. The esters were hydrolysed to the corresponding acids without any isomerization using lithium hydroxide in ethanol–water at room temperature. The acids were subjected to biological screening. We are particularly interested in compounds inhibiting the enzymes cyclooxygenase (COX-2) and 5-lipoxygenase (5-LO). Some of the results have been reported[11] and further results will be reported elsewhere in due course.

We have devised a synthetic strategy to obtain the oxygen- and sulfur-containing polyunsaturated fatty acids involving the degradation of naturally occurring fatty acids, EPA and DHA, as the main feature. The overall yields to the epoxides are high, but unfortunately the subsequent oxidative cleavage to the aldehydes proceeded with unsatisfactory yields. Work is in progress aimed at improving this reaction. Although the yields are not optimized we believe the current strategy competes well with those based on multi-step construction of the acids from simpler starting material. An additional advantage is the complete conservation of the *Z*-configuration of the appropriate double bonds, originating from the fatty acids EPA and DHA, throughout the syntheses.

Experimental

The NMR spectra were recorded for samples in $CDCl_3$ with a Varian Gemini 200, Bruker Avance DPX 200, Bruker Avance DPX 300, or Bruker Avance DRX 500 instrument. IR spectra were obtained with a Perkin–Elmer 1310 or a Nicolet Magna-IR 550 infrared spectrometer. Mass spectra under were recorded at 70 eV with a Fisons VG Pro spectrometer. Dichloromethane and acetonitrile were dried by distillation over calcium hydride. Methanol was dried over magnesium.

all-(Z)-6-Iodo-8,11,14,17-eicosatetraen-5-olide (**3**) was prepared from acid **1** essentially as described in the literature (Ref. 6), in 95% yield, and used without further purification. ^1H NMR (200 MHz): δ 0.92 (t, *J* 7.5 Hz, 3 H), 1.67–2.12 (m, 6 H), 2.21–2.68 (m, 2 H), 2.69–2.90 (m, 8 H), 3.82–3.97 (m, 1 H), 3.99–4.14 (m, 1 H), 5.16–5.60 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 18.1 (CH_2), 20.4 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.8 (CH_2), 27.9 (CH_2), 29.4 (CH_2), 34.3 (CH_2), 36.9 (CH), 80.7 (CH), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.6 (CH), 128.5 (CH), 128.6 (CH), 131.2 (CH), 131.9 (CH), 170.3 (CO). IR (film): 3011 (s), 2962 (s), 2932 (m), 1736 (s) cm^{-1}. MS (EI): *m/z* 428 (0.2, M^+), 301 (49), 79 (100). HRMS: Found, 428.122722; calc. for $C_{20}H_{29}IO_2$, 428.121232.

all-(Z)-Methyl 5,6-epoxy-8,11,14,17-eicosatetraenoate (**4**). To a stirred solution of the crude iodolactone **3** (25.7 g, 0.060 mol) in methanol (310 ml) was added K_2CO_3 (12.5 g, 0.090 mol). After 3 h at room temperature water was added, and the product extracted with hexane. The extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the epoxide **4** (18.1 g, 91%) which was used without further purification. ^1H NMR (200 MHz): δ 0.93 (t, *J* 7.5 Hz, 3 H), 1.42–1.68 (m, 2 H), 1.68–1.90 (m, 2 H), 2.03 (m, 2 H), 2.12–2.49 (m, 4 H), 2.65–2.82, (m, 6 H), 2.82–2.96 (m, 2 H), 3.63 (s, 3 H), 5.15–5.58 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 21.9 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 27.1 (CH_2), 33.5 (CH_2), 51.5 (CH_3), 56.1 (CH), 56.4 (CH), 124.2 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 130.5 (CH), 131.9 (CH), 173.5 (CO). IR (film): 3013 (s), 2964 (s), 2873 (m), 1740 (s) cm^{-1}. MS (EI): *m/z* 332 (0.3, M^+), 79 (100). HRMS: Found, 332.236911; calc. for $C_{21}H_{32}O_3$, 332.235145.

all-(Z)-1,1-Dimethoxy-3,6,9,12-pentadecatetraene (**6**). Periodic acid (13.7, 0.060 mol) was added to a stirred solution of the epoxide **4** (17.9 g, 0.054 mol) in dry methanol (350 ml). After 6 h at room temperature water was added and the solution was extracted with hexane. The extract was washed with water and brine prior to drying ($MgSO_4$). Evaporation of solvents followed by flash chromatography of the residue (silica gel, hexane–

EtOAc 95:5) gave the acetal **6** (6.4 g, 45%) as a colourless oil. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.37 (m, 2 H), 2.68–2.92 (m, 6 H), 3.30 (s, 6 H), 4.35 (t, *J* 5.8 Hz, 1 H), 5.19–5.54 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.4 (CH_3), 20.7 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 31.1 (CH_2), 52.9 (CH_3), 103.8 (CH), 123.5 (CH), 126.6 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 129.9 (CH), 131.6 (CH). IR (film): 3013 (s), 2963 (s), 2933 (m) cm^{-1}.

all-(Z)-3,6,9,12-Pentadecatetraenal (**5**). A solution of 80% aq. formic acid (12 ml) was added to a stirred solution of acetal **6** (0.92 g, 3.5 mmol) in dioxane (10 ml) at room temperature. After 1.5 h water was added, and the solution extracted with hexane. The extract was neutralized with saturated aq. $NaHCO_3$, washed with brine and dried ($MgSO_4$). Evaporation of the solvents gave aldehyde **5** (0.72 g, 95%). ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.03 (m, 2 H), 2.62–2.94 (m, 6 H), 3.12–3.26 (m, 2 H), 5.18–5.46 (m, 6 H), 5.47–5.74 (m, 2 H), 9.63 (t, *J* 1.8 Hz, 1 H). ^{13}C NMR (50 MHz): δ 14.4 (CH_3), 20.7 (CH_2), 25.7 (CH_2), 25.8 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 42.5 (CH_2), 118.4 (CH), 126.5 (CH), 126.7 (CH), 127.2 (CH), 128.3 (CH), 128.5 (CH), 131.7 (CH), 132.7 (CH), 198.5 (CO). IR (film): 3013 (s), 2965 (s), 2933 (m), 1728 (s) cm^{-1}.

Reduction of aldehydes. General procedure. An ice-cooled solution of aldehyde (1 equiv.) in methanol (3 ml per mmol) was treated with a solution of $NaBH_4$ (2.6 equiv.) in methanol (1.5 ml per mmol). The reaction was stirred for 30 min after which 1.4 M hydrochloric acid (1.5 ml per mmol $NaBH_4$) was added, and the mixture was extracted with hexane–ether 2:1. The extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 8:2).

all-(Z)-3,6,9,12-Pentadecatetraen-1-ol (**7**) was obtained by reduction of the aldehyde **5** in 78% yield. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.72 (s, 1 H), 2.05 (m, 2 H), 2.33 (m, 2 H), 2.68–2.94 (m, 6 H), 3.62 (t, *J* 6.5 Hz, 2 H), 5.19–5.59 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 31.3 (CH_2), 62.3 (CH_2), 125.0 (CH), 126.3 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.9 (CH), 130.3 (CH), 131.3 (CH). IR (film): 3331 (br s), 3013 (s), 2963 (s), 2933 (m) cm^{-1}. MS (EI): *m/z* 220 (0.3, M^+), 79 (100). HRMS: Found, 220.180895; calc. for $C_{15}H_{24}O$, 220.182716.

Preparation of bromides. General procedure. Bromine (1.1 equiv.) was added dropwise to an ice-cooled suspension of Ph_3P (1.3 equiv.) in acetonitrile (2 ml per mmol Ph_3P), followed by a solution of the alcohol (1 equiv.) and pyridine (1.5 equiv.) in acetonitrile (0.5 ml per mmol alcohol). After 1 h, hexane was added. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was passed through a short pad of silica gel which was subsequently rinsed with hexane.

all-(Z)-1-Bromo-3,6,9,12-pentadecatetraene (**8**) was obtained from the alcohol **7** in 85% yield. ^{1}H NMR (200 MHz): δ 0.96 (t, *J* 7.5 Hz, 3 H), 2.06 (m, 2 H), 2.63 (m, 2 H), 2.69–2.89 (m, 6 H), 3.36 (t, *J* 7.1 Hz, 2 H), 5.16–5.60 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 30.8 (CH_2), 32.3 (CH_2), 126.3 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 128.6 (CH), 130.9 (CH), 132.0 (CH). IR (film): 3013 (s), 2964 (s), 2932 (m) cm^{-1}.

Preparation of the thia-acids. General procedure. Lithium hydroxide (1.9 equiv.) was added to a stirred solution of methyl mercaptoacetate, methyl 3-mercaptopropionate or γ-thiobutyrolactone (1.4 equiv.) in methanol (11 ml per mmol of bromide). After 15 min at room temperature the bromide (1 equiv.) dissolved in methanol (0.3 ml per mmol of bromide) was added, and the mixture stirred at room temperature. The reaction was monitored by GC or TLC; the time required for completion is indicated for each compound. After completion, water was added and the solution extracted with ether. The extract was washed with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue purified by flash chromatography (silica gel, hexane–EtOAc 95:5).

Ester hydrolysis. General procedure. A solution of the ester (1 equiv.) in methanol (3 ml per mmol of ester) was added to a solution of lithium hydroxide (6.5 equiv.) in water (3 ml per mmol of ester). Unreacted ester was removed by extraction with hexane. The water phase was acidified with dilute hydrochloric acid to pH 2 and extracted with hexane–ethyl acetate (3:1). The extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the acid.

all-(Z)-3-Thia-6,9,12,15-octadecatatraenoic acid (**9b**). Reaction of the bromide **8** and methyl mercaptoacetate gave *all-(Z)-methyl 3-thia-6,9,12,15-octadecatatraenate* (**9a**, 71%). The reaction time was 5 h. ^{1}H NMR (200 MHz): δ 0.93 (t, *J* 7.5 Hz, 3 H), 2.03 (m, 2 H), 2.25–2.42 (m, 2 H), 2.63 (t, *J* 7.6 Hz, 2 H), 2.70–2.89 (m, 6 H), 3.20 (s, 2 H), 3.68 (s, 3 H), 5.17–5.62 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.8 (CH_3), 21.0 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 27.3 (CH_2), 32.8 (CH_2), 33.7 (CH_2), 52.5 (CH_2), 126.3 (CH), 126.7 (CH), 127.1 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 129.0 (CH), 131.2 (CH), 169.7 (CO). IR (film): 3012 (s), 2963 (s), 2932 (m), 1738 (s) cm^{-1}. MS (EI): *m/z* 308 (5, M^+), 235 (14), 202 (5), 79 (100). HRMS: Found, 308.181476; calc. for $C_{18}H_{28}O_2S$, 308.181002.

Hydrolysis gave the acid **9b** in 95% yield. The reaction time was 4 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 2.05 (m, 2 H), 2.27–2.48 (m, 2 H), 2.69 (t, *J* 7.3 Hz, 2 H), 2.73–2.92 (m, 6 H), 3.24 (s, 2 H), 5.20–5.55

(m, 8 H), 11,84 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.8 (CH_3), 21.0 (CH_2), 26.0 (CH_2), 26.01 (CH_2), 27.2 (CH_2), 32.8 (CH_2), 33.7 (CH_2), 126.4 (CH), 126.8 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 129.3 (CH), 131.4 (CH), 176.2 (CO). IR (film): 3012 (s), 2964 (s), 2931 (m), 1709 (s) cm^{-1}. MS (EI): *m/z* 294 (7, M^+), 235 (20), 79 (100). HRMS: Found, 294.163273; calc. for $C_{17}H_{26}O_2S$, 294.165352.

all-(Z)-4-Thia-7,10,13,16-nonadecatatraenoic acid (**10b**). Reaction of the bromide **8** and methyl mercaptopropionate gave *all-(Z)-methyl 4-thia-7,10,13,16-nonadecatatraenoate* (**10a**, 70%). The reaction time was 6 h. ^{1}H NMR (300 MHz): δ 0.93 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.24–2.38 (m, 2 H), 2.48–2.61 (m, 4 H), 2.67–2.83 (m, 8 H), 3.65 (s, 3 H), 5.12–5.48 (m, 8 H). ^{13}C NMR (75 MHz): δ 14.2 (CH_3), 20.4 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.9 (CH_2), 27.4 (CH_2), 31.9 (CH_2), 34.6 (CH_2), 51.6 (CH_3), 126.9 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 129.4 (CH), 131.9 (CH), 172.2 (CO). IR (film): 3012 (s), 2963 (s), 2932 (s), 1741 (s) cm^{-1}. MS (EI): *m/z* 322 (14, M^+), 291 (9), 235 (24), 79 (100). HRMS: Found, 322.193594; calc. for $C_{19}H_{30}O_2S$, 322.196652.

Hydrolysis gave the acid **10b** in 96% yield. The reaction time was 7 h. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.05 (m, 2 H), 2.23–2.44 (m, 2 H), 2.60–2.70 (m, 4 H), 2.70–2.93 (m, 8 H), 5.19–5.52 (m, 8 H), 11.20 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 32.4 (CH_2), 35.1 (CH_2), 126.3 (CH), 127.0 (CH), 127.1 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 128.8 (CH), 131.2 (CH), 177.2 (CO). IR (film): 3012 (s), 2964 (s), 2932 (m), 1712 (s) cm^{-1}. MS (EI): *m/z* 308 (5, M^+), 235 (13), 202 (4), 173 (6), 79 (100). HRMS: Found, 308.182164; calc. for $C_{18}H_{28}O_2S$, 308.181002.

all-(Z)-5-Thia-8,11,14,17-eicosatetraenoic acid (**11b**). Reaction of the bromide **8** and γ-thiobutyrolactone gave *all-(Z)-methyl 5-thia-8,11,14,17-eicosatetraenoate* (**11a**, 82%). The reaction time was 8 h. ^{1}H NMR (500 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.88 (m, 2 H), 2.04 (m, 2 H), 2.28–2.35 (m, 2 H), 2.41 (t, *J* 7.3 Hz, 2 H), 2.51 (t, *J* 7.5 Hz, 2 H), 2.54 (t, *J* 7.3 Hz, 2 H), 2.75–2.85 (m, 6 H), 3.64 (s, 3 H), 5.23–5.45 (m, 8 H). ^{13}C NMR (125 MHz): δ 14.2 (CH_3), 20.9 (CH_2), 24.6 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 27.4 (CH_2), 31.3 (CH_2), 31.7 (CH_2), 32.7 (CH_2), 51.5 (CH_3), 126.9 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 129.3 (CH), 131.9 (CH), 173.5 (CO). IR (film): 3012 (s), 2962 (s), 2932 (s), 1740 (s) cm^{-1}. MS (EI): *m/z* 336(17, M^+), 235 (25), 202 (6), 79 (100). HRMS: Found, 336.212245; calc. for $C_{20}H_{32}O_2S$, 336.212302.

Hydrolysis gave the acid **11b** in 85% yield. The reaction time was 8 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.89 (m, 2 H), 1.97–2.15 (m, 2 H), 2.24–2.41 (m, 2 H), 2.41–2.63 (m, 6 H), 2.66–2.92 (m, 6 H), 5.18–5.52 (m, 8 H), 11.53 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.8 (CH_3), 21.0 (CH_2), 24.7 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 27.8 (CH_2), 31.6 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 126.5 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.9 (CH), 131.5 (CH), 178.8 (CO). IR (film): 3012 (s), 2963 (s), 2932 (s), 1709 (s) cm^{-1}. MS (EI): *m/z* 322 (7, M^+), 253 (6), 235 (19), 79 (100). HRMS: Found, 322.197729; calc. for $C_{19}H_{30}O_2S$, 322.196652.

all-(Z)-5-Iodo-7,10,13,16,19-docosapentaen-4-olide (**12**) was prepared from the acid **2** essentially as desribed in the literature (Refs. 6, 7) in 95% yield. The spectral data (^{1}H NMR and IR) were in agreement with those of the literature (Ref. 7). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.4 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.5 (CH_2), 25.7 (CH_2), 27.2 (CH_2), 28.3 (CH_2), 34.5 (CH_2), 37.8 (CH), 80.5 (CH), 126.6 (CH), 126.8 (CH), 127.2 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 131.3 (CH), 131.8 (CH), 176.1 (CO).

all-(Z)-Methyl 4,5-epoxy-7,10,13,16,19-docosapentaenoate (**13**). The reaction of iodolactone **12** with base was carried out as described for **4** giving the crude epoxide **13** in 93% yield. The spectral data (^{1}H NMR and IR) were in agreement with those of the literature (Ref. 9). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 23.3 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 26.1 (CH_2), 30.9 (CH_2), 51.6 (CH_3), 55.9 (CH), 56.5 (CH), 124.1 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 130.6 (CH), 131.9 (CH), 173.1 (CO).

all-(Z)-1,1-Dimethoxy-3,6,9,12,15-octadecapentaene (**16**). The reaction of epoxide **13** was carried out as described for **6** furnishing the acetal **16** in 46% yield. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.38 (m, 2 H), 2.69–2.92 (m, 8 H), 3.30 (s, 6 H), 4.36 (t, *J* 8.0 Hz, 1 H), 5.19–5.55 (m, 10 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 52.8 (CH_3), 103.9 (CH), 123.8 (CH), 126.9 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 130.1 (CH), 131.9 (CH). IR (film): 3012 (s), 2960 (s), 2935 (m) cm^{-1}.

all-(Z)-3,6,9,12,15-Octadecapentaenal (**15**). The acetal **16** was hydrolysed as described for **5** furnishing the aldehyde **15** in 96% yield. The spectral data (^{1}H NMR and IR) were in agreement with those of the literature (Ref. 9). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 42.8 (CH_2), 118.1 (CH), 126.3 (CH), 126.4 (CH), 127.1 (CH), 127.1 (CH), 127.7 (CH), 127.9 (CH), 128.1 (CH), 131.3 (CH), 132.3 (CH), 197.7 (CO).

all-(Z)-3,6,9,12,15-Octadecapentaen-1-ol (**17**). Reduction of the aldehyde **15** gave the alcohol **17** in 80% yield. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.76 (s, 1 H), 2.04 (m, 2 H), 2.31 (m, 2 H), 2.67–2.90 (m, 8 H),

3.61 (t, *J* 6.5 Hz, 2 H), 5.19–5.59 (m, 10 H). ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 20.6 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 30.8 (CH_2), 62.0 (CH_2), 125.4 (CH), 126.6 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 130.5 (CH), 131.6 (CH). IR (film): 3405 (br s), 3012 (s), 2962 (s), 2933 (m) cm^{-1}. MS (EI): *m/z* 260 (0.5 M^+), 79 (100). HRMS: Found, 260.213554; calc. for $C_{18}H_{28}O$, 260.214016.

all-(Z)-1-Bromo-3,6,9,12,15-octadecapentaene (**18**). The compound was prepared from the alcohol **17** in 84% yield. ^{1}H NMR (200 MHz): δ 0.96 (t, *J* 7.5 Hz, 3 H), 2.06 (m, 2 H), 2.63 (m, 2 H), 2.71–2.97 (m, 8 H), 3.36 (t, *J* 7.1 Hz, 2 H), 5.20–5.62 (m, 10 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 31.3 (CH_2), 32.8 (CH_2), 125.7 (CH), 126.3 (CH), 127.0 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 130.1 (CH), 131.3 (CH). IR (film): 3013 (s), 2964 (s), 2932 (m) cm^{-1}.

all-(Z)-3-Thia-6,9,12,15,18-heneicosapentaenoic acid (**19b**). Reaction of the bromide **18** with methyl mercaptoacetate gave *all-(Z)-methyl 3-thia-6,9,12,15,18-heneicosapentaenoate* (**19a**, 81%). The reaction time was 5 h. ^{1}H NMR (200 MHz): δ 0.93 (t, *J* 7.5 Hz, 3 H), 2.03 (m, 2 H), 2.26–2.42 (m, 2 H), 2.63 (t, *J* 7.4 Hz, 2 H), 2.69–2.91 (m, 8 H), 3.21 (s, 2 H), 3.70 (s, 3 H), 5.19–5.50 (m, 10 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.4 (CH_2), 32.9 (CH_2), 33.9 (CH_2), 52.5 (CH_3), 126.3 (CH), 126.8 (CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 129.0 (CH), 131.3 (CH), 169.7 (CO). IR (film): 3012 (s), 2963 (s), 2932 (m), 1736 (s) cm^{-1}. MS (EI): *m/z* 348 (2, M^+), 275 (10), 79 (100). HRMS: Found, 348.210739; calc. for $C_{21}H_{32}O_2S$, 348.212302.

Hydrolysis gave the acid **19b** in 96% yield. The reaction time was 3 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 2.05 (m, 2 H), 2.29–2.46 (m, 2 H), 2.69 (t, *J* 7.3 Hz, 2 H), 2.72–2.96 (m, 8 H), 3.23 (s, 2 H), 5.20–5.55 (m, 10 H), 11.34 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.4 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 126.3 (CH), 126.7 (CH), 127.2 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 129.1 (CH), 131.3 (CH), 175.7 (CO). IR (film): 3012 (s), 2964 (s), 2931 (m), 1709 (s) cm^{-1}. MS (EI): *m/z* 334 (0.5, M^+), 275 (7), 79 (100). HRMS: Found, 334.197702; calc. for $C_{20}H_{30}O_2S$, 334.196652.

Preparation of the oxa-acids. General procedure. A solution of $BF_3 \cdot Et_2O$ (0.35 equiv.) in dry dichloromethane (4.5 ml per mmol of $BF_3 \cdot Et_2O$) was added dropwise over a period of 50 min to an ice-cooled mixture of alcohol (1 equiv.) and ethyl diazoacetate (1.3 equiv.) in dry dichloromethane (7 ml per mmol of alcohol). The mixture was stirred at room temperature. The reaction was monitored by GC and TLC and the time required for completion is indicated below for each compound. After completion, 0.05 M hydrochloric acid (6 ml per mmol of diazoacetate) was added and the water phase was extracted with chloroform. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography (silca gel, hexane–EtOAc 95:5).

all-(Z)-3-Oxa-6,9,12,15-octadecatetraenoic acid (**20b**). Reaction of the alcohol **7** with ethyl diazoacetate gave *all-(Z)-ethyl 3-oxa-6,9,12,15-octadecatatraenoate* (**20a**, 51%). The reaction time was 1.5 h. ^{1}H NMR (200 MHz): δ 0.92 (t, *J* 7.5 Hz, 3 H), 1.23 (t, *J* 7.1 Hz, 3 H), 2.02 (m, 2 H), 2.29–2.47 (m, 2 H), 2.67–2.91 (m, 6 H), 3.50 (t, *J* 7.0 Hz, 2 H), 4.03 (s, 2 H), 4.16 (q, *J* 7.1 Hz, 2 H), 5.17–5.52 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.8 (CH_3), 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.3 (CH_2), 60.9 (CH_2), 68.3 (CH_2), 71.2 (CH_2), 124.8 (CH), 126.3 (CH), 127.1 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 129.3 (CH), 131.2 (CH), 169.2 (CO). IR (film): 3013 (s), 2964 (s), 2931 (m), 1756 (s), 1735 (m) cm^{-1}. MS (EI): *m/z* 306 (0.8, M^+), 202 (6), 79 (100). HRMS: Found, 306.217815; calc. for $C_{19}H_{30}O_3$, 306.219495.

Hydrolysis gave acid **20b** in 93% yield. The reaction time was 1.5 h. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.31–2.47 (m, 2 H), 2.68–2.90 (m, 6 H), 3.55 (t, *J* 6.9 Hz, 2 H), 4.11 (s, 2 H), 5.19–5.55 (m, 8 H), 10.89 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.2 (CH_2), 67.7 (CH_2), 71.4 (CH_2), 124.6 (CH), 126.3 (CH), 127.1 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 129.6 (CH), 131.3 (CH), 174.5 (CO). IR (film): 3013 (s), 2963 (s), 2933 (m), 1732 (s) cm^{-1}. MS (EI): *m/z* 278 (2, M^+), 202 (2), 79 (100). HRMS: Found, 278.190428; calc. for $C_{17}H_{26}O_3$, 278.188195.

all-(Z)-3-Oxa-6,9,12,15,18-heneicosapentaenoic acid (**21b**). Reaction of the alcohol **17** with ethyl diazoacetate gave *all-(Z)-ethyl 3-oxa-6,9,12,15,18-heneicosapentaenoate* (**21a**, 50%). The reaction time was 2 h. ^{1}H NMR (200 MHz): δ 0.92 (t, *J* 7.5 Hz, 3 H), 1.23 (t, *J* 7.1 Hz, 3 H), 2.02 (m, 2 H), 2.29–2.46 (m, 2 H), 2.63–2.93 (m, 8 H), 3.50 (t, *J* 6.9 Hz, 2 H), 4.02 (s, 2 H), 4.17 (q, *J* 7.1 Hz, 2 H), 5.16–5.52 (m, 10 H). ^{13}C NMR (50 MHz): δ 14.1 (CH_3), 14.2 (CH_3), 20.4 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 27.7 (CH_2), 60.6 (CH_2), 68.2 (CH_2), 71.1 (CH_3), 125.4 (CH), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 129.9 (CH), 131.8 (CH) 170.3 (C=O). IR (film): 3013 (s), 2964 (s), 2932 (s), 1755 (s), 1735 (m) cm^{-1}. MS (EI): *m/z* 346 (0.3, M^+), 242 (1), 213 (3), 79 (100). HRMS: Found, 346.250315; calc. for $C_{22}H_{34}O_3$, 346.250795.

Hydrolysis gave the acid **21b** in 92% yield. The reaction time was 1.5 h. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.31–2.50 (m, 2 H), 2.68–2.95 (m, 6 H), 3.55 (t, 2 H, *J* 6.9 Hz, 2 H), 4.11 (s, 2 H), 5.18–5.62 (m, 10 H), 10.90 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.7

(CH_2), 27.6 (CH_2), 67.7 (CH_2), 71.3 (CH_2), 125.2 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.0. (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 130.3 (CH), 131.9 (CH), 175.4 (CO). IR (film): 3012 (s), 2965 (s), 1727 (s) cm^{-1}. MS (EI): *m/z* 318 (0.1, M^+), 79 (100). HRMS: Found, 318.220679; calc. for $C_{20}H_{30}O_3$, 318.219495.

(2E,6Z,9Z,12Z)-Pentadeca-2,6,9,12-tetraenal (**22**). A mixture of periodic acid (12.8 g, 0.056 mol) in dry ether (465 ml) was stirred for 1 h. The mixture was filtered and epoxide **4** (9.3 g, 0.028 mol) was added to the filtrate. After being stirred for 2 h at room temperature the reaction mixture was filtered, and the filtrate washed with water until neutral and dried ($MgSO_4$). Evaporation of the solvent gave a crude mixture containing the aldehyde **5**. The mixture was dissolved in ether (250 ml) and DBU (0.5 ml) was added. The solution was stirred for 30 min, then washed with water until neutral and dried ($MgSO_4$). The solution was concentrated under reduced pressure and the residue filtered through a 4 cm plug of silica gel (hexane–EtOAc 95:5 as the eluent) to give the aldehyde **22** (2.4 g, 40%). ^1H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 2.02 (m, 2 H), 2.26 (m, 2 H), 2.35 (m, 2 H), 2.68–2.88 (m, 4 H), 5.19–5.52 (m, 6 H), 6.11 (ddt, *J* 1.4 Hz, *J* 7.8 Hz, *J* 15.6 Hz, 1 H), 6.81 (dt, *J* 6.4 Hz, *J* 15.6 Hz, 1 H), 9.49 (d, *J* 7.8 Hz, 1 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 32.6 (CH_2), 126.9 (CH), 127.5 (CH), 127.8 (CH), 128.7 (CH), 129.5 (CH), 132.1 (CH), 133.3 (CH), 157.7 (CH), 193.9 (CO). IR (film): 3012 (s), 2964 (s), 2933 (m), 1694 (s) cm^{-1}. MS (EI): *m/z* 218 (1, M^+), 79 (100), 67 (76). HRMS: Found, 218.166547; calc. for $C_{15}H_{22}O$, 218.167066.

(2E,6Z,9Z,12Z,15Z)-Octadeca-2,6,9,12,15-pentaenal (**23**). Oxidative cleavage of epoxide **13** followed by DBU induced isomerization, as described for aldehyde **22**, furnished the aldehyde **23** in 41% yield. ^1H NMR (200 MHz): δ 0.93 (t, *J* 7.5 Hz, 3 H), 2.03 (m, 2 H), 2.27 (m, 2 H), 2.36 (m, 2 H), 2.65–2.94 (m, 6 H), 5.17–5.52 (m, 8 H), 6.11 (ddt, *J* 1.4 Hz, *J* 7.9 Hz, *J* 15.6 Hz, 1 H), 6.81 (dt, *J* 6.4 Hz, *J* 15.6 Hz, 1 H), 9.49 (d, *J* 7.9 Hz, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 33.0 (CH_2), 126.2 (CH), 127.0 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.9 (CH), 128.7 (CH), 131.3 (CH), 132.5 (CH), 156.6 (CH), 192.4 (CO). IR (film): 3012 (s), 2964 (s), 2933 (m), 1694 (s) cm^{-1}. MS (EI): *m/z* 258 (0.7, M^+), 79 (100). HRMS: Found, 258.196424; calc. for $C_{18}H_{26}O$, 258.198366.

(2E,6Z,9Z,12Z)-Pentadeca-2,6,9,12-tetraen-1-ol (**24**). Reduction of the aldehyde **22** gave the alcohol **24** in 82% yield. ^1H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.56 (s, 1 H), 1.96–2.22 (m, 6 H), 2.69–2.87 (m, 4 H), 4.05 (d, *J* 4.3 Hz, 2 H), 5.19–5.47 (m, 6 H), 5.53–5.78 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.8 (CH_2), 32.1 (CH_2), 63.6 (CH_2), 127.0 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 129.4 (CH), 132.0 (CH), 132.4 (CH). IR (film): 3329 (br s), 3012 (s), 2962 (s), 2939 (m) cm^{-1}. MS (EI): *m/z* 220 (0.5, M^+) 79 (100). HRMS: Found, 220.182135; calc. for $C_{15}H_{24}O$, 220.182716.

(2E,6Z,9Z,12Z,15Z)-Octadeca-2,6,9,12,15-pentaen-1-ol (**25**). Reduction of the aldehyde **23** gave the alcohol **25** in 85% yield. ^1H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.52 (s, 1 H), 1.95–2.23 (m, 6 H), 2.69–2.91 (m, 6 H), 4.05 (d, *J* 4.4 Hz, 2 H), 5.19–5.50 (m, 6 H), 5.59–5.71 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 21.2 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 32.6 (CH_2), 63.7 (CH_2), 126.3 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 128.7 (CH), 131.3 (CH), 132.7 (CH). IR (film): 3320 (br s), 3012 (s), 2963 (s), 2932 (m) cm^{-1}. MS (EI): *m/z* 260 (0.2, M^+), 79 (100). HRMS: Found, 260.212853; calc. for $C_{18}H_{28}O$, 260.214016.

(2E,6Z,9Z,12Z) - 1 - Bromopentadeca - 2,6,9,12 - tetraene (**26**). The bromide was prepared from the alcohol **24** in 85% yield. ^1H NMR (200 MHz): δ 0.96 (t, *J* 7.5 Hz, 3 H), 1.96–2.23 (m, 6 H), 2.67–2.89 (m, 4 H), 3.92 (d, *J* 6.5 Hz, 2 H), 5.19–5.48 (m, 6 H), 5.58–5.86 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 27.1 (CH_2), 32.5 (CH_2), 33.8 (CH_2), 126.2 (CH), 126.4 (CH), 127.3 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 131.3 (CH), 134.9 (CH). IR (film): 3011 (s), 2963 (s), 2932 (m) cm^{-1}.

(2E,6Z,9Z,12Z,15Z) - 1 - Bromooctadeca - 2,6,9,12,15-pentaene (**27**). The bromide was prepared from the alcohol **25** in 83% yield. ^1H NMR (200 MHz): δ 0.96 (t, *J* 7.5 Hz, 3 H), 1.97–2.23 (m, 6 H), 2.68–2.94 (m, 6 H), 3.92 (d, *J* 6.5 Hz, 2 H), 5.19–5.48 (m, 8 H), 5.59–5.86 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 27.1 (CH_2), 32.5 (CH_2), 33.8 (CH_2), 126.2 (CH), 126.4 (CH), 127.2 (CH), 127.4 (CH), 127.51 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 131.3 (CH), 134.9 (CH). IR (film): 3012 (s), 2963 (s), 2932 (m) cm^{-1}.

(5E,9Z,12Z,15Z) - 3 - Thiaoctadeca - 5,9,12,15 - tetraenoic acid (**28b**). Reaction of the bromide **26** and methyl mercaptoacetate gave *(5E,9Z,12Z,15Z)-methyl 3-thiaoctadeca-5,9,12,15-tetraenoate* (**28a**, 72%). The reaction time was 3.5 h. ^1H NMR (500 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 2.04 (m, 2 H), 2.06–2.17 (m, 4 H), 2.77 (m, 4 H), 3.13 (s, 2 H), 3.16 (d, *J* 7.3 Hz, 2 H), 3.68 (s, 3 H), 5.24–5.41 (m, 7 H), 5.51–5.58 (m, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 27.4 (CH_2), 31.8 (CH_2), 32.6 (CH_2), 34.5 (CH_2), 52.4 (CH_3), 126.2 (CH), 126.3 (CH), 127.2 (CH), 127.6 (CH), 128.3 (CH), 131.2 (CH), 133.6 (CH), 169.7 (CO). IR (film): 3011 (s), 2962 (s), 2933 (m), 1739 (s) cm^{-1}. MS (EI): *m/z* 308 (1.5, M^+), 235 (40), 202 (39), 79 (100). HRMS: Found, 308.179377; calc. for $C_{18}H_{28}O_2S$, 308.181002.

Hydrolysis gave the acid **28b** in 95% yield. The reaction time was 12 h. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.95–2.23 (m, 6 H), 2.78 (m, 4 H), 3.15 (s, 2 H), 3.19 (d, *J* 7.0 Hz, 2 H), 5.19–5.43 (m, 7 H), 5.44–5.63 (m, 1 H), 12.40 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.9 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 34.2 (CH_2), 124.6 (CH), 126.9 (CH), 127.8 (CH), 128.3 (CH), 128.34 (CH), 128.9 (CH), 131.8 (CH), 134.7 (CH), 177.1 (CO). IR (film): 3010 (s), 2965 (s), 1707 (s) cm^{-1}. MS (EI): *m/z* 294 (0.3, M^+), 235 (6), 203 (7), 79 (100). HRMS: Found, 294.167011; calc. for $C_{17}H_{26}O_2S$, 294.165352.

(6E,10Z,13Z,16Z) - 4 - Thianonadeca - 6,10,13,16 - tetraenoic acid (**29b**). Reaction of the bromide **26** and methyl mercaptoacetate gave *(6E,10Z,13Z,16Z)-methyl 4-thianonadeca-6,10,13,16-tetraenoate* (**29a**, 72%). The reaction time was 3.5 h. ^{1}H NMR (200 MHz): δ 0.9 (t, *J* 7.5 Hz, 3 H), 1.94–2.20 (m, 6 H), 2.47–2.60 (m, 2 H), 2.61–2.87 (m, 6 H), 3.07 (d, *J* 6.2 Hz, 2 H), 3.65 (s, 3 H), 5.18–5.60 (m, 8 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 27.5 (CH_2), 32.6 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 51.9 (CH_3), 125.5 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 131.3 (CH), 132.5 (CH), 171.2 (CO). IR (film): 3010 (s), 2958 (s), 2931 (m), 1738 (s) cm^{-1}. MS (EI): *m/z* 322 (0.5, M^+), 235 (7), 202 (6), 79 (100). HRMS: Found, 322.196220; calc. for $C_{19}H_{30}O_2S$, 322.196652.

Hydrolysis gave the acid **29b** in 85% yield. The reaction time was 12 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.91–2.23 (m, 6 H), 2.52–2.72 (m, 4 H), 2.73–2.88 (m, 4 H), 3.09 (d, *J* 6.2 Hz, 2 H), 5.15–5.62 (m, 8 H), 11,62 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 20.5 (CH_2), 24.9 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.9 (CH_2), 32.2 (CH_2), 33.9 (CH_2), 34.4 (CH_2), 126.0 (CH), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.1 (CH), 131.9 (CH), 133.3 (CH), 178.4 (CO). IR (film): 3011 (s), 2963 (s), 2932 (s), 1712 (s) cm^{-1}. MS (EI): *m/z* 308 (0.4, M^+), 235 (6), 202 (7), 79 (100). HRMS: Found, 308.181365; calc. for $C_{18}H_{28}O_2S$, 308.181002.

(7E,11Z,14Z,17Z) - 5 - Thiaeicosa - 7,11,14,17 - tetraenoic acid (**30b**). Reaction of the bromide **26** and γ-thiobutyrolactone gave *(7E,11Z,14Z,17Z)-methyl 5-thiaeicosa-7,11,14,17-tetraenoate* (**30a**, 70%). The reaction time was 6 h. ^{1}H NMR (300 MHz): δ 0.92 (t, *J* 7.5 Hz, 3 H), 1.83 (m, 2 H), 1.95–2.17 (m, 6 H), 2.38 (t, *J* 7.5 Hz, 2 H), 2.43 (t, *J* 7.2 Hz, 2 H), 2.65–2.84 (m, 6 H), 3.03 (d, *J* 6.6, 2 H), 3.62 (s, 3 H), 5.25–5.74 (m, 8 H). ^{13}C NMR (75 MHz): δ 14.2 (CH_3), 20.4 (CH_2), 24.2 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 26.9 (CH_2), 29.6 (CH_2), 32.1 (CH_2), 32.6 (CH_2), 33.4 (CH_2), 51.4 (CH_3), 126.2 (CH), 126.9 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.1 (CH), 131.8 (CH), 132.8 (CH), 173.4 (CO). IR (film): 3011 (s), 2961 (s), 2933 (s), 1740 (s) cm^{-1}. MS (EI): *m/z* 336(3, M^+), 235 (15), 202 (17), 79 (100). HRMS: Found, 336.212956; calc. for $C_{20}H_{32}O_2S$, 336.212302.

Hydrolysis gave the acid **30b** in 83% yield. The reaction time was 12 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.86 (m, 2 H), 1.94–2.22 (m, 6 H), 2.47 (t, *J* 7.3 Hz, 2 H), 2.48 (t, *J* 7.1 Hz, 2 H), 2.78 (m, 6 H), 3.06 (d, *J* 6.2 Hz, 2 H), 5.20–5.63 (m, 8 H), 11.50 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.2 (CH_2), 24.6 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 27.6 (CH_2), 30.1 (CH_2), 32.7 (CH_2), 33.2 (CH_2), 34.0 (CH_2), 125.6 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 131.3 (CH), 132.3 (CH), 178.5 (CO). IR (film): 3011 (s), 2963 (s), 2932 (s), 1709 (s) cm^{-1}. MS (EI): *m/z* 322 (3, M^+), 235 (14), 202 (13), 79 (100). HRMS: Found, 322.196033; calc. for $C_{19}H_{30}O_2S$, 322.196652.

(5E,9Z,12Z,15Z,18Z) - 3 - Thiaheneicosa - 5,9,12,15,18-pentaenoic acid (**31b**). Reaction of the bromide **27** and methyl mercaptoacetate gave *(5E,9Z,12Z,15Z,18Z)-methyl 3-thiaheneicosa-5,9,12,15,18-pentaenoate* (**31a**, 70%). The reaction time was 3 h. ^{1}H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.95–2.21 (m, 6 H), 2.67–2.91 (m, 6 H), 3.13 (s, 2 H), 3.16 (d, *J* 7.0 Hz, 2 H), 3.69 (s, 3 H), 5.18–5.46 (m, 9 H), 5.47–5.63 (m, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2) 26.3 (CH_2), 27.5 (CH_2), 32.0 (CH_2), 32.7 (CH_2), 34.7 (CH_2), 52.5 (CH_3), 124.3 (CH), 126.3 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 131.3 (CH), 133.7 (CH), 169.8 (CO). IR (film): 3012 (s), 2962 (s), 2933 (m), 1739 (s) cm^{-1}. MS (EI): *m/z* 348 (1, M^+), 275 (8), 243 (15), 79 (100). HRMS: Found, 348.212091; calc. for $C_{21}H_{32}O_2S$, 348.212302.

Hydrolysis gave the acid **31b** in 95% yield. The reaction time was 10 h. ^{1}H NMR (200 MHz): δ 0.95 (t, *J* 7.5 Hz, 3 H), 1.95–2.23 (m, 6 H), 2.67–2.92 (m, 6 H), 3.16 (s, 2 H), 3.20 (d, *J* 7.1 Hz, 2 H), 5.20–5.44 (m, 9 H), 5.45–5.63 (m, 1 H), 11.81 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 20.5 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 31.3 (CH_2), 32.2 (CH_2) 34.2 (CH_2), 124.6 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 131.9 (CH), 134.7 (CH), 177.3 (CO). IR (film): 3011 (s), 2963 (s), 2931 (m), 1708 (s) cm^{-1}. MS (EI): *m/z* 334 (0.4, M^+), 275 (3), 243 (6), 79 (100). HRMS: Found, 334.196864; calc. for $C_{20}H_{30}O_2S$, 334.196652.

(5E,9Z,12Z,15Z) - 3 - Oxaoctadeca - 5,9,12,15 - tetraenoic acid (**32b**). Reaction of the alcohol **24** with ethyl diazoacetate gave *(5E,9Z,12Z,15Z)-ethyl 3-oxaoctadeca-5,9,12,15-tetraenoate* (**32a**, 50%). The reaction time was 1.5 h. ^{1}H NMR (200 MHz): δ 0.92 (t, *J* 7.5 Hz, 3 H), 1.23 (t, *J* 7.1 Hz, 3 H), 1.92–2.20 (m, 4 H), 2.65–2.85 (m, 4 H), 3.93–4.05 (d + s, 4 H), 4.17 (q, *J* 7.1 Hz, 2 H), 5.16–5.43 (m, 6 H), 5.44–5.78 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.5 (CH_3), 20.8 (CH_2), 25.7 (CH_2), 25.8 (CH_2), 26.9 (CH_2), 32.4 (CH_2), 60.8 (CH_2), 66.8 (CH_2),

71.9 (CH_2), 125.3 (CH), 126.5 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 131.5 (CH), 134.8 (CH), 169.7 (CO). IR (film): 3011 (s), 2964 (s), 2934 (s), 1756 (s), 1735 (m) cm^{-1}. MS (EI): *m/z* 306 (0.1, M^+), 202 (3), 79 (100). HRMS: Found, 306.220613; calc. for $C_{19}H_{30}O_3$, 306.219495.

Hydrolysis gave the acid **32b** in 92% yield. The reaction time was 1.5 h. ^1H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.94–2.22 (m, 4 H), 2.68–2.86 (m, 2 H), 4.02 (d, *J* 6.1 Hz, 2 H), 4.08 (s, 2 H), 5.17–5.42 (m, 6 H), 5.43–5.81 (m, 2 H), 10.72 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.6 (CH_3), 20.8 (CH_2), 25.8 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 32.4 (CH_2), 66.1 (CH_2), 72.1 (CH_2), 124.9 (CH), 126.5 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 131.5 (CH), 135.4 (CH), 175.1 (CO). IR (film): 3011 (s), 2963 (s), 2933 (s), 1732 (s) cm^{-1}. MS (EI): *m/z* 278 (0.2, M^+), 202 (2), 79 (100). HRMS: Found, 278.187609; calc. for $C_{17}H_{26}O_3$, 278.188195.

(5E,9Z,12Z,15Z,18Z) - 3 - Oxaheneicosa - 5,9,12,15,18-pentaenoic acid (**33b**). Reaction of the alcohol **25** with ethyl diazoacetate gave *(5E,9Z,12Z,15Z,18Z)-ethyl 3-oxaheneicosa-5,9,12,15,18-pentaenoate* (**33a**, 49%). The reaction time was 2 h. ^1H NMR (200 MHz): δ 0.91 (t, *J* 7.5 Hz, 3 H), 1.22 (t, *J* 7.1 Hz, 3 H), 1.92–2.19 (m, 4 H), 2.65–2.88 (m, 4 H), 3.93–4.04 (d+s, 4 H), 4.15 (q, *J* 7.1 Hz, 2 H), 5.18–5.42 (m, 8 H), 5.43–5.78 (m, 2 H). ^{13}C NMR (50 MHz): δ 14.4 (CH_3), 20.7 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 26.0 (CH_2), 26.8 (CH_2), 32.3 (CH_2), 60.7 (CH_2), 66.7 (CH_2), 71.8 (CH_2), 125.3 (CH), 126.5 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.6 (CH), 131.4 (CH), 134.7 (CH), 169.7 (CO). IR (film): 3012 (s), 2964 (s), 2933 (m), 1756 (s), 1735 (m) cm^{-1}. MS (EI): *m/z* 346 (0.1, M^+), 213 (4), 79 (100). HRMS: Found, 346.249049; calc. for $C_{22}H_{34}O_3$, 346.250795.

Hydrolysis gave the acid **33b** in 94% yield. The reaction time was 1.5 h. ^1H NMR (200 MHz): δ 0.94 (t, *J* 7.5 Hz, 3 H), 1.93–2.22 (m, 4 H), 2.67–2.92 (m, 4 H), 4.02 (d, *J* 6.0 Hz, 2 H), 4.08 (s, 2 H), 5.19–5.44 (m, 8 H), 5.45–5.82 (m, 2 H), 10.97 (br s, 1 H). ^{13}C NMR (50 MHz): δ 14.9 (CH_3), 21.1 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 27.2 (CH_2), 32.7 (CH_2), 66.2 (CH_2), 72.1 (CH_2), 124.7 (CH), 126.3 (CH), 127.2 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 131.3 (CH), 135.1 (CH), 174.6 (CO). IR (film): 3012 (s), 2964 (s), 2933 (s), 1732(s) cm^{-1}. MS (EI): *m/z* 318 (1, M^+), 213 (4), 79 (100). HRMS: Found, 318.218282; calc. for $C_{20}H_{30}O_3$, 318.219495.

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