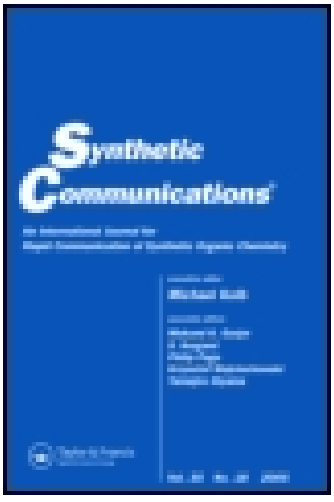

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Syntheses of Some Sulfur-Containing Polyunsaturated Fatty Acids as Potential Lipoxygenase Inhibitors

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Syntheses of Some Sulfur-Containing Polyunsaturated Fatty Acids as Potential Lipoxygenase Inhibitors

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Abstract: Starting from (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid (EPA) and (all-*Z*)-4,7,10,13,16,19-docosahexaenoic acid (DHA), several polyunsaturated fatty acids, containing a sulfur atom either in the chain or in a thiophene ring, have been synthesized as potential inhibitors of lipoxygenases.

Keywords: polyunsaturated fatty acids, sulfur-containing fatty acids, 5-lipoxygenase, dicyclohexylborane

INTRODUCTION

Leukotrienes are final products from the oxidation of arachidonic acid, a polyunsaturated ω-6 fatty acid. It is well established that leukotrienes, particularly LTB_4, are important mediators of widespread inflammatory diseases as bronchial asthma, rheumatoid arthritis, gout, and psoriasis.[1] Consequently, it is not surprising that considerable research effort has been targeted at the development of drugs that inhibit the formation of leukotrienes.[2] Among the primary targets are inhibitors of 5-lipoxygenase (5-LO), an enzyme that starts the cascade of oxidation steps leading to a number of structurally different

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leukotrienes. The same oxidative enzymes also convert the ω-3 polyunsaturated acid eicosapentaenoic acid (**1**, EPA) into the corresponding leukotrienes, which diverge structurally from those derived from arachidonic acid only by an additional *Z*-double bond. However, the biological properties of these leukotrienes differ from those derived from arachidonic acid in several respects, particularly by not being such strong mediators of inflammation. The competition with arachidonic acid for 5-LO may explain why EPA acts as a weak inhibitor of this enzyme and consequently its ant-iinflammatory properties.[3,4]

The initial reaction of 5-LO with either arachidonic acid or EPA seems to be hydrogen abstraction at carbon-7. Corey et al.[5] substituted the methylene group at this position in arachidonic acid with sulfur, and the resulting compound **2** possessed inhibitory activity for 5-LO. Later, Hanko et al.[6] synthesized and tested for 5-LO inhibition several analogs of arachidonic acid containing a sulfur atom at the 5-position. Structure–activity studies concluded that the sulfur atom should preferably be attached to a conjugated diene moiety as in compound **3**, the most active 5-LO inhibitor of those tested (Fig. 1).

We have prepared several analogs of EPA and docosahexaenoic acid (**4**, DHA) that incorporate a sulfur atom at different positions in the molecules.[7,8] Some of these compounds have shown interesting biological activity, particularly as inhibitors of the enzymes $cPLA_2$ and COX-2.[9,10] Considering the available biological data, it seemed interesting to prepare the vinyl sulfides **5** and **6** and the thiophene derivatives **7** and **8** as potential lipoxygenase inhibitors. The present article describes our synthetic effort toward this goal starting from EPA and DHA (Fig. 2).

RESULTS AND DISCUSSION

We expected to obtain the vinyl sulfides **5** and **6** by selective reduction of the corresponding acetylenic esters **9** and **10**. The syntheses are outlined in Scheme 1. The aldehydes **11** and **12**, which were available in 75% overall yields by oxidative degradation of EPA and DHA, respectively,[7] were

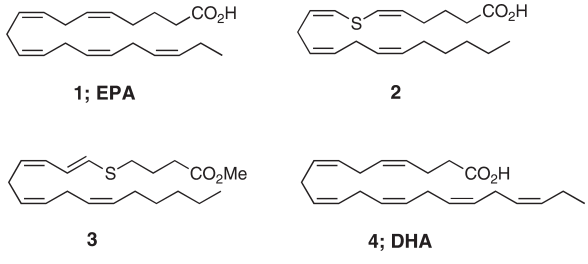


Figure 1. Structures of the natural PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and two previously synthesized sulfur-containing analogues of arachidonic acid.

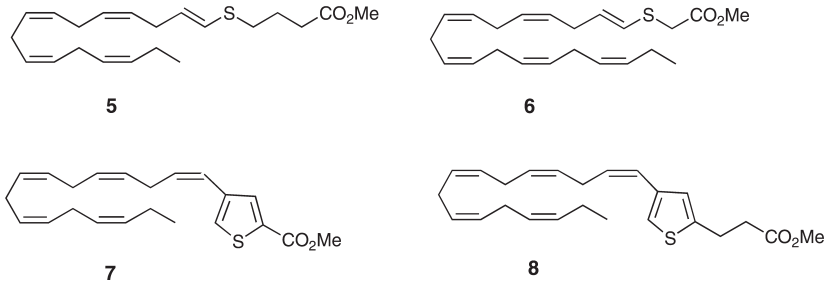
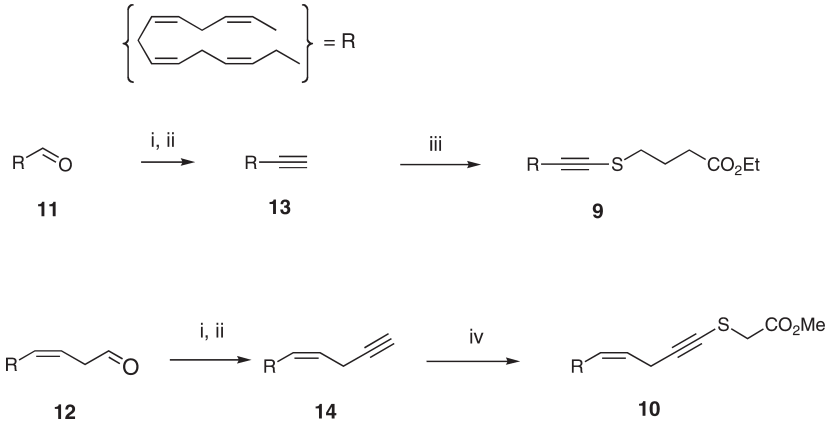


Figure 2. Structures of some sulfur-containing ω-3 PUFAs.

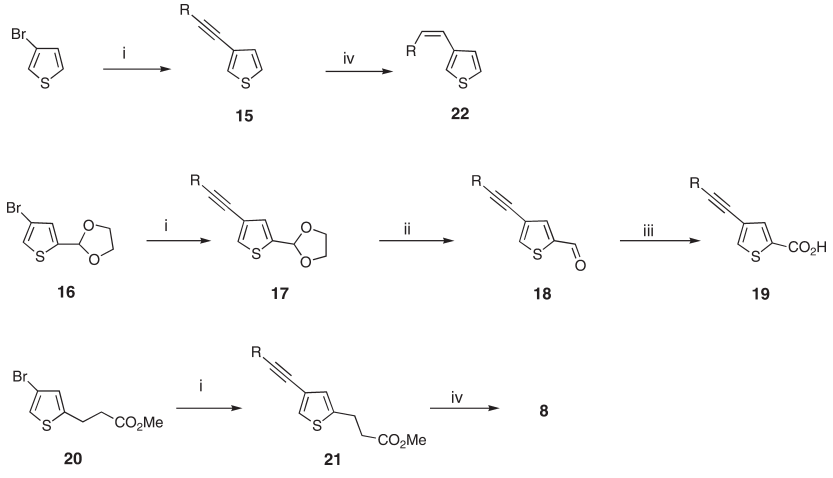
converted to the corresponding acetylenic derivatives **13** and **14** by treatment of the respective gem. dibromoolefin with methylithium.[11] In a one-pot reaction, the lithium derivative of **13** was subjected to elemental sulfur and ethyl 4-iodobutanoate, furnishing the ester **9** in 40% yield. A similar reaction sequence transformed the acetylene **14** with sulfur and methyl bromoacetate into the ester **10** in 67% yield. Finally, selective reduction of the acetylenic bond of each of the esters should have provided the target compounds. However, several hydrogenation methods were tried without success. Only when the reduction was carried out with dicyclohexylborane in THF[12] were the esters **5** and **6** were present in the reaction products, but we were unable to separate them from other components of the reaction mixtures.

The synthetic strategy to the thiophene derivatives **7** and **8** also involved as the last step the selective reduction of the corresponding acetylenic



Scheme 1. Reagents and conditions: (i) CBr_4, Ph_3P, Zn, CH_2Cl_2; (ii) MeLi, -78°C; (iii) (a) BuLi, S_8, $-78-20^\circ$C; (b) ethyl 4-iodobutanoate, $0-20^\circ$C; (iv) (a) BuLi, S_8, $-78-20^\circ$C; (b) methyl bromoacetate $0-20^\circ$C.

derivatives, which we anticipated to obtain by Pd(0)-catalyzed coupling of a 3-halothiophene derivative with the appropriate polyenyne (Scheme 2).[13] With respect to the functionality at the 2-position of the thiophene ring, it could either be introduced after the coupling reaction or be present in the halothiophene derivative. Initially we opted for the first alternative, rendering the synthesis of the thiophene derivative **15** as our first objective. The Pd(0)-catalyzed coupling of 3-bromothiophene with the tetraenyne **13** proceeded as expected, furnishing the thiophene derivative **15** in 58% yield. In the subsequent reaction with alkylithium, a selective hydrogen–lithium exchange at the 5-position of the thiophene ring was not achieved; the reaction of **15** with butylithium at −78°C followed by quenching with solid carbon dioxide and acidification gave a mixture of acids in a disappointingly poor yield. The result was equally unsatisfactory when the lithium derivative was quenched with 2-(2-bromoethyl)-1,3-dioxolane, en route to the ester **8**. Hence, we abandoned this approach in preference for coupling the acetylene with an appropriately substituted bromothiophene derivative. Methyl 4-bromothiophene-2-carboxylate was prepared from 2,4-dibromothiophene according to the literature,[14] but the Pd(0)-catalyzed coupling with the acetylene **13** was not satisfactory. On the other hand, coupling of the ethylene acetal of commercially available 4-bromo-2-thiophenecarboxaldehyde (**16**) with the acetylene proceeded smoothly to give compound **17** in 94% yield. Subsequent hydrolysis to the aldehyde **18** followed by silver nitrate oxidation furnished the acid **19** in 80% overall yield. Methyl 3-(4-bromo-2-thienyl)propanoate (**20**), prepared from the corresponding commercially available acrylic acid derivative by esterification and Rh-catalyzed hydrogenation, underwent Pd(0)-catalyzed coupling with the acetylene **13** to give the



Scheme 2. Reagents and conditions: (i) **13**, MeLi, Pd(0), −78°C; (ii) HCO_2H, H_2O; (iii) Ag_dO; (iv) dicyclohexenylborane-Me_2S.

thienyl ester **21** in 93% yield. It now remained to reduce selectively the triple bond to a *Z*-double bond, but again this transformation caused problems. To find satisfactory conditions, compound **15** was used as model substrate. Although several methods gave none or very little of the expected product, reaction of this compound with the dicyclohexylborane–dimethylsulfide complex in THF[12] afforded the all-*Z* polyene **22** in 50% yield. However, when this procedure was applied to the ester **21**, the thiophene derivative **8** was obtained in a disappointing 20% yield.

The biological testing of the polyunsaturated fatty acid derivatives is in progress, and the results will be reported elsewhere in due course.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 instrument, a Bruker Avance DPX 200 instrument, a Bruker Avance DPX 300 instrument, or a Bruker Avance DRX 500 instrument. 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.

Dichloromethane and acetonitrile were dried by distillation over calcium hydride. Methanol was dried over magnesium. 3-Bromothiophene, 4-bromothiophene-2-carboxaldehyde, methyl (*E*)-3-(4-bromo-2-thienyl)acrylate, ethyl 4-iodobutanoate, and 2-(2-bromoethyl)-1,3-dioxalane were obtained commercially.

(all-*Z*)-4,7,10,13-hexadecatetraen-1-yne (13)

A mixture of zinc powder (2.40 g, 37 mmol), Ph_3P (9.69 g, 37 mmol), and CBr_4 (12.26 g, 37 mmol) in CH_2Cl_2 (100 ml) was stirred at rt for 40 h. A solution of the aldehyde **11**[7] (4.0 g, 18 mmol) in CH_2Cl_2 (20 ml) was added. After stirring for 1 h at rt, the mixture was filtered and the solvent partially evaporated under reduced pressure. The residue was filtered through a plug of silica gel (hexane as eluent) to give the dibromide (6.58 g, 96%) as an oil. δ_H (200 MHz) 0.98 (t, *J* 7.5 Hz, 3H), 2.06 (m, 2H), 2.6–3.0 (m, 8H), 5.2–5.6 (m, 8H), 6.35 (t, *J* 7.2 Hz, 1H); δ_C (50 MHz) 14.8 (CH_3), 21.1, 26.1, 26.2, 26.3, 31.8 (CH_2), 89.2 (CBr_2), 123.6, 126.4, 126.9, 127.1 (CH), 128.1 (2 × CH), 129.7, 131.4, 135.9 (3 × CH=). MeLi (10 ml, 1.6 M, 16 mmol) was added to a stirred solution of the dibromide (5.0 g, 13 mmol) in dry ether (60 ml) at −78°C. After 1 h, water was added, and the mixture extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane) to give the acetylene **13** (2.44 g, 85%) as an oil. ν_{max} (film)/cm^{-1} 3268, 2985, 2935, 2100, 1632,

1420; δ_H (200 MHz) 0.96 (t, *J* 7.5 Hz, 3H), 1.96 (t, *J* 2.7 Hz, 1H), 2.06 (m, 2H), 2.7–2.9 (m, 6H), 2.9-3.0 (m, 2H), 5.2–5.6 (m, 8H); δ_C (50 MHz) 14.7 (CH_3), 17.3, 20.9 (CH_2), 25.9 (2 × CH_2), 26.1 (CH_2), 68.2 (CH), 82.4 (C), 123.6, 126.5, 126.8, 127.2, 128.1, 128.2, 129.6, 131.5 (CH); m/z (EI): 214 (M^+, 0.2%), 117, 91, 79 (100). (HRMS: found: M^+ 214.1703. $C_{16}H_{22}$ requires 214.1722).

(all-*Z*)-4,7,10,13,16-nonadecapentaen-1-yne (14)

Reaction of the aldehyde **12**[7] by the procedure described for **13** gave the acetylene **14** as an oil in 78% yield. ν_{max} (film)/cm^{-1} 3285, 3000, 2950, 2120, 1645, 1430; δ_H (200 MHz) 0.96 (t, *J* 7.5 Hz, 3H), 1.96 (t, *J* 2.7 Hz, 1H), 2.06 (m, 2H), 2.7–2.9 (m, 8H), 2.9–3.0 (m, 2H), 5.3–5.5 (m, 10H); δ_C (75 MHz) 14.3 (CH_3), 16.9, 20.6 (CH_2), 25.5 (2 × CH_2), 25.6 (2 × CH_2), 68.1 (CH), 82.5 (C), 124.1, 127.0, 127.4, 127.8, 127.9, 128.4, 128.6, 128.7, 130.1, 132.0 (CH); *m/z* (EI) 254 (M^+, 15%), 117, 91, 79 (100). (HRMS found: M^+ 254.2022. $C_{19}H_{26}$ requires 254.2035).

Acetylenic Sulfides: General Procedure

n-BuLi (1 equiv.) was added to a solution of the acetylene (1 equiv.) in dry ether (0.3 mmol/ml) at −78°C. The mixture was stirred at this temperature for 30 min before addition of elemental sulphur (1.3 equiv.). The reaction mixture was slowly warmed to rt and stirred for 1 h. Then the halide was added to the mixture at 0°C. After stirring for 30 min at 0°C and 2 h at room temperature, the mixture was poured into water and the phases separated. The aq. phase was extracted with ether. The combined ether extract was washed with brine and water and then dried ($MgSO_4$). Evaporation of solvents under reduced pressure followed by flash chromatography of the residue on silica gel (95:5 hexane/EtOAc) gave the pure product.

Ethyl (all-*Z*)-5-thia-9,12,15,18-heneicosapentaen-6-ynoate (9)

This was obtained as an oil in 40% yield by reaction of the acetylene **13** with sulfur and ethyl 4-iodobutanoate according to the general procedure. ν_{max} (film)/cm^{-1} 2990, 2950, 1730, 1200; δ_H (300 MHz) 0.95 (t, *J* 7.5 Hz, 3H), 1.24 (t, *J* 7.1 Hz, 3H), 2.03 (m, 4H), 2.45 (t, *J* 7.3 Hz, 2H), 2.70 (t, *J* 7.0 Hz, 2H), 2.8–2.9 (m, 6H), 3.06 (d, *J* 4.9 Hz, 2H), 4.11 (q, *J* 7.1 Hz, 2 H), 5.3–5.5 (m, 8H); δ_C (75 MHz) 14.2, 14.3 (CH_3), 18.6, 20.6, 24.4 (CH_2), 25.5 (2 × CH_2), 25.6, 32.4, 34.5 (CH_2), 60.4 (OCH_2), 68.0, 92.1 (C), 124.2, 126.9, 127.4, 127.7, 128.7, 128.8, 129.7, 132.1 (CH) 172.9 (C═O)

m/z (EI) 360 (M^+, 2.2%), 245, 87 (100). (HRMS found: M^+ 360.2115. $C_{22}H_{32}O_2S$ requires 360.2123).

Methyl (all-*Z*)-3-thia-7,10,13,16,19-docosapentaen-4-ynoate (10)

This was obtained as an oil in 43% yield by reaction of the acetylene **14** with sulfur and methyl bromoacetate according to the general procedure. ν_{max} (film)/cm^{-1} 2990, 2940, 1730, 1430, 1270; δ_H (300 MHz) 0.95 (t, *J* 7.5 Hz, 3H), 2.04 (m, 2H), 2.7–2.9 (m, 8H), 3.05 (d, *J* 5.5 Hz, 2H), 3.43 (s, 2H), 3.72 (s, 3H), 5.3–5.5 (m, 10H); δ_C (75 MHz) 14.2 (CH_3), 18.5, 20.5 (CH_2), 25.5 (2 × CH_2), 25.6 (2 × CH_2), 37.2 (CH_2), 52.6 (OCH_3), 66.7, 93.8 (2 × C), 123.9, 126.9, 127.3, 127.7, 127.8, 128.3, 128.5, 128.6, 129.9, 131.9 (CH), 168.9 (C═O); *m/z* (EI) 358 (M^+, 1.78%), 299, 285, 91 (100). (HRMS found: $M^+ - 59$ 299.1830; $C_{20}H_{27}S$ requires 299.1833. Found $M^+ - 73$ 285.1676; $C_{19}H_{25}S$ requires 285.1677).

(all-*Z*)-1-(3-thienyl)-4,7,10,13-hexadecatetraen-1-yne (15)

A mixture of the acetylene **13** (1.2 g, 5.6 mmol), 3-bromothiophene (0.92 g, 5.6 mmol), 10% Pd-C (0.24 g), CuI (41 mg, 0.22 mmol), Ph_3P (230 mg, 0.88 mmol), and Et_3N (15 ml) in dry acetonitrile (7.5 ml) was heated under reflux for 40 h, while the reaction was monitored by gas chromatography (GC). After cooling, the reaction mixture was filtered through Celite®, and solvents were evaporated. The residue was purified by flash-chromatography (hexane) to give the thiophene **15** (0.96 g, 58%) as an oil. ν_{max}(film)/cm^{-1} 2983, 2938, 2905, 1378, 1260, 1140; δ_H (200 MHz): 0.96 (t, *J* 7.5 Hz, 3H), 2.06 (m, 2H), 2.6–3.0 (m, 6H), 3.15 (d, *J* 4.1 Hz, 2H), 5.2–5.6 (m, 8H), 7.1–7.2 (m, 1H), 7.2–7.3 (m, 1H), 7.4–7.5 (m, 1H); δ_C (50 MHz): 14.3 (CH_3), 17.8, 20.6, 25.5 (CH_2), 25.6 (2 × CH_2), 75.5, 87.5, 122.6 (C), 124.3, 124.9, 126.9, 127.4, 127.6, 127.7, 128.5, 128.6, 129.8, 129.9, 132.0 (CH); m/z (EI): 296 (M^+, 1.5%), 227, 108, 91, 79 (100). (HRMS found: M^+ 296.1586. $C_{20}H_{24}S$ requires 296.1599).

(all-*Z*)-4-(4,7,10,13-hexadecatetraen-1-ynyl)-2-(1,3-dioxolanyl) thiophene (17)

A mixture of the acetylene **13** (1.0 g, 4.67 mmol), the thienyl acetal **16**[15] (440 mg, 1.87 mmol), 10% Pd-C (200 mg), CuI (40 mg), Ph_3P (250 mg), and triethylamine (25 ml) in dry acetonitrile (15 ml) was heated under reflux for 75 h while monitoring the reaction by GC. After cooling to rt, the reaction mixture was filtered through Celite®, and solvents evaporated. Flashchromatography of the residue (9:1 hexane/CH_2Cl_2) recovered

unreacted acetylene (450 mg), and further elution (9:1 hexane/EtOAc) gave compound **17** (650 mg, 94%) as an oil. ν_{max}(film)/cm^{-1} 3012, 2940, 2962, 1438, 1231, 1155; δ_H (300 MHz): 0.96 (t, 3H, *J* 7.5 Hz), 2.06 (m, 2H), 2.7–2.9 (m, 6H), 3.13 (d, *J* 5.5 Hz, 2H), 3.9–4.1 (m, 4H), 5.3–5.6 (m, 8H), 6.02 (s, 1H), 7.09 (m, 1H), 7.31 (m, 1H); δ_C (75 MHz): 14.2 (CH_3), 17.7, 20.5 (CH_2), 25.5 (3 × CH_2), 65.1 (2 × CH_2O), 75.3, 87.2 (C), 99.7 (O-C-O), 122.3 (C), 124.2, 126.9, 127.3, 127.7, 128.5, 128.6 (CH), 128.8 (2 × CH), 129.8, 131.9 (CH), 141.5 (C); m/z (EI): 368 (M^+, 7.1%), 299, 182, 108, 91, 79 (100), (HRMS found: M^+ 368.1825. $C_{23}H_{28}O_2S$ requires 368.1810).

(all-*Z*)-4-(4,7,10,13-hexadecatetraen-1-ynyl)thiophene-2-carboxaldehyde (18)

Aqueous formic acid (80%, 10 ml) was added to a solution of the acetal **17** (510 mg, 1.4 mmol) in dioxane (15 ml). The solution was stirred for 1 h at rt. Water was added, and the mixture was extracted with ether. The extract was washed with saturated aq. $NaHCO_3$ and dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography (95:5 hexane/EtOAc) gave the aldehyde **18** (400 mg, 90%) as an oil. ν_{max}(film)/cm^{-1} 3020, 2985, 2943, 1682, 1446, 1238, 1163; δ_H (200 MHz): 0.94 (t, *J* 7.5 Hz, 3H), 2.04 (m, 2 H), 2.7–2.9 (m, 6H), 3.15 (d, *J* 4.8 Hz, 2H), 5.2–5.6 (m, 8H), 7.67 (s, 2H), 9.83 (d, *J* 0.7 Hz, 1H); δ_C (50 MHz): 14.2 (CH_3), 17.7, 20.5, 25.4 (CH_2), 25.5 (2 × CH_2), 74.0, 89.0 (C), 123.6 (CH), 124.3 (C), 126.8, 127.2, 127.6, 128.6, 128.7, 130.2, 132.0, 136.5, 138.5 (CH), 143.1 (C), 182.4 (C═O); m/z (EI): 324 (M^+, 3.2%), 307, 295, 187, 115, 108, 91, 79 (100). (HRMS found: M^+ 324.1567. $C_{21}H_{24}OS$ requires 324.1548).

(all-*Z*)-4-(4,7,10,13-hexadecatetraen-1-ynyl)thiophene-2-carboxylic Acid (19)

To a vigorously stirred solution of NaOH (150 mg, 3.8 mmol) in water (3 ml), a solution of $AgNO_3$ (330 mg, 1.9 mmol) in water (3 ml) was added. The mixture was cooled in an ice bath before a solution of the aldehyde **18** (310 mg, 0.96 mmol) in dioxane (2 ml) was added. After stirring for 20 min, water and ether were added. The organic phase was separated, and the water phase was acidified with 5% aq. HCl and extracted with ether. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give the acid **19** (290 mg, 89%) as an oil. ν_{max}(film)/cm^{-1} 3028, 2981, 1688, 1455, 1276; δ_H (200 MHz): 0.96 (t, *J* 7.5 Hz, 3H), 2.06 (m, 2H), 2.7–2.8 (m, 6H), 3.16 (d, *J* 4.8 Hz, 2H), 5.2–5.9 (m, 8H), 7.58 (m, 1H), 7.81 (m, 1H), 11.7 (br s, 1H); δ_C (50 MHz): 14.9 (CH_3), 18.4, 21.1 (CH_2), 26.1 (3 × CH_2), 74.3, 88.5 (C), 123.3 (CH), 123.5 (C), 126.3, 126.7, 127.1, 128.1, 128.2, 129.6, 131.4 (CH), 131.7 (C), 135.0, 136.8 (CH), 182.4

(C═O); m/z (EI): 340 (M^+, 0.6%), 307, 283, 115, 108, 91, 79 (100), (HRMS found: M^+ 340.1518. $C_{21}H_{24}O_2S$ requires 340.1497).

Methyl 3-(4-Bromo-2-thienyl)-propanoate (20)

To a solution of 3-(4-bromo-2-thienyl)-propenoic acid (2.50 g, 10.7 mmol) in methanol/benzene (1:1, 80 ml), conc. H_2SO_4 (1 ml) was added, and the mixture was heated under reflux for 4 h. The mixture was washed successively with saturated aq. $NaHCO_3$ and brine, then dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The crude ester was dissolved in benzene (60 ml) and hydrogenated on a Parr apparatus using $(Ph_3P)_3RhCl$ (0.5 g) as catalyst. After 10 and 20 h, additional amounts of catalyst (0.5 g) were added, and ethanol (10 ml) was added as well. After 30 h, the mixture was filtered through Celite®, and the solvents were evaporated under reduced pressure. Purification of the residue by flash chromatography (8:2 hexane/EtOAc) gave the ester **20** (1.75 g, 66%) as an oil. ν_{max}(film)/cm^{-1} 2915, 1739, 1427, 1171; δ_H (300 MHz) 2.63 (t, *J* 7.5 Hz, 2H), 3.08 (t, *J* 7.5 Hz, 2H), 3.66 (s, 3H), 6.71 (m, 1H), 6.99 (m, 1H); δ_C (75 MHz) 25.3, 35.6 (CH_2), 52.1 (OCH_3), 109.8 (C), 121.6, 128.2 (CH═), 145.3 (C), 173.5 (C═O); m/z (EI): 250/248 (M^+, 50.6/55.8%), 190/188, 177/175, 43 (100). (HRMS: found: M^+ 247.9495. $C_8H_9BrO_2S$ requires 247.9506).

Methyl 3-[4-(all-*Z*-4,7,10,13,16-hexadecapentaenyl)-2-thienyl]propanoate (21)

Reaction of the acetylene **13** with the bromide **20** was carried out as described for compound **17** to give the ester **21** in 93% yield, as an oil. ν_{max}(film)/cm^{-1} 3010, 2955, 2925, 1733, 1434, 1195, 1170; δ_H (200 MHz): 0.95 (t, *J* 7.5 Hz, 3H), 2.06 (m, 2H), 2.63 (t, *J* 7.3 Hz, 2H), 2.7–3.0 (m, 6H), 3.0–3.2 (m, 4H), 3.67 (s, 3H), 5.2–5.6 m, 8H), 6.77 (m, 1H), 7.13 (m, 1H); δ_C (50 MHz): 14.3 (CH_3), 17.8, 20.6, 25.1 (CH_2), 26.0 (3 × CH_2), 35.5 (CH_2), 51.7 (CH_3O), 75.7, 86.9, 121.7 (C), 123.8, 125.6, 126.3 (CH), 126.8 (2 × CH), 127.1, 127.9, 128.0, 129.1, 131.3 (CH), 141.8 (C), 171.4 (C═O); m/z (EI): 382 (M^+, 5.4%), 313, 199, 187, 91, 79, 73 (100). (HRMS found: M^+ 382.1951. $C_{24}H_{30}O_2S$ requires 382.1967).

(all-*Z*)-1-(3-thienyl)-4,7,10,13,16-hexadecapentaene (22)

Cyclohexene (0.18 ml, 1.77 mmol) was added dropwise to an ice-cooled solution of borane-dimethylsulfide complex (8 M; 0.10 ml, 0.77 mmol) in dry THF (4.0 ml). The resulting mixture was left stirring at rt for 2 h and cooled to 0°C before a solution of **15** (100 mg, 0.34 mmol) in dry THF (1.0 ml) was added. The mixture was allowed to reach rt during 1 h and

stirred for an additional 2 h. Acetic acid (0.5 ml) was then added dropwise, and the resulting mixture was left stirring overnight. The mixture was cooled to 0°C, and aq. NaOH (2 M, 5.0 ml) was slowly added followed by dropwise addition of 50% aq. H_2O_2 (0.30 ml). The mixture was extracted with ether. The extract was washed with water and brine and then dried ($MgSO_4$). Solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography (9:1 hexane/EtOAc) to give the all-*Z* polyene **22** (50 mg, 50%), as an oil. ν_{max}(film)/cm^{-1} 2933, 2922, 1436, 1161; δ_H (200 MHz): 0.95 (t, *J* 7.5 Hz, 3H), 2.05 (m, 2H), 2.7–2.9 (m, 6H), 3.0–3.2 (m, 2H), 5.2–5.7 (m, 9H), 6.26 (dt, *J* 1.7, 11.4 Hz, 1H), 7.0–7.2 (m, 2H), 7.2–7.3 (m, 1H); δ_C (50 MHz): 14.7 (CH_3), 20.9, 25.6, 25.7, 25.8, 26.1 (CH_2), 121.0, 125.3, 126.0, 126.5, 126.6, 127.5 (CH), 127.6 (2 × CH), 128.0, 128.2, 128.5, 129.3, 131.5 (CH), 137.9 (C). (HRMS found: M^+ 298.1751. $C_{20}H_{26}S$ requires 298.1755).

Methyl 3-[4-(all-*Z*-4,7,10,13,16-hexadecapentaenyl)-2-thienyl]propanoate (8)

Cyclohexene (0.38 ml, 3.71 mmol) was added dropwise to an ice-cooled solution of borane–dimethylsulfide complex (8 M; 0.24 ml, 1.84 mmol) in dry THF (4.0 ml). The resulting mixture was left stirring at rt for 2 h and cooled to 0°C before a solution of the ester **21** (500 mg, 1.31 mmol) in dry THF (2.0 ml) was added. The mixture was allowed to reach rt over 1 h and stirred for an additional 2.5 h. AcOH (1.06 ml) was then added dropwise, and the resulting mixture was left stirring overnight. The mixture was cooled to 0°C, and aq. NaOH (2.0 M, 7.2 ml) was added slowly, followed by dropwise addition of 30% aq. H_2O_2 (0.70 ml). The mixture was extracted with ether. The extract was washed with water and brine and then dried ($MgSO_4$). Solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography (9:1 hexane/EtOAc) to give the ester **8** (100 mg, 20%) as an oil. δ_H (200 MHz): 0.95 (t, *J* 7.5 Hz, 3H), 2.05 (m, 2H), 2.67 (t, *J* 7.5 Hz, 2H), 2.6–2.9 (m, 6H), 3.0–3.2 (m, 4H), 3.67 (s, 3H), 5.2–5.6 (m, 9H), 6.26 (dt, *J* 1.5, 11.4 Hz, 1H), 6.80 (d, *J* 1.0 Hz, 1H), 6.94 (s, 1H); δ_C (50 MHz): 14.7 (CH_3), 20.9, 25.6, 25.8, 25.9, 26.1, 27.7, 30.0 (CH_2), 51.9 (OCH_3), 120.9, 123.3, 126.0, 126.6 (CH), 127.5 (2 × CH), 127.6, 128.0, 128.2, 128.5, 129.3, 131.7 (CH), 137.9, 142.2 (C), 172.1 (C═O); m/z (EI): 384 (M^+, 35.2%), 313, 183, 147, 135, 108, 91, 79. (HRMS found: M^+ 384.2109. $C_{24}H_{32}O_2S$ requires 384.2123).

REFERENCES

1. (a) Henderson, W. R., Jr. The role of leukotrienes in inflammation. *Ann. Intern. Med.* **1994**, *121*, 684–697; (b) Fitzpatrick, F. A.; Lepley, R.; Orning, L.;

Duffin, K. Effects of leukotriene A4 on nutrophil activation. *Ann. NY Acad. Sci.* **1994**, *714*, 64–74.
2. Drazen, J. M.; Israel, E.; ÓByrne, P. M. *Drug Therapy* **1999**, *340*, 197–206.
3. Kinsella, J. E. B.; Lokesh, B.; Stone, R. A. Dietary n-3 polyunsaturated fatty acids and amelioration of cardiovascular disease: possible mechanisms. *Am. J. Clin. Nutr.* **1990**, *52*, 1–28.
4. Horrobin, D. F. Abnormal membrane concentrations of 20 and 22-carbon essential fatty acids: A common link between risk factors and coronary and peripheral vascular disease? *Prostaglandins Leukotrienes Essential Fatty Acids* **1995**, *53*, 385–396.
5. Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. R. A new class of irreversible inhibitors of leukotriene biosynthesis. *J. Am. Chem. Soc.* **1985**, *107*, 713–715.
6. Hanko, R.; Hammond, M. D.; Fruchtmann, R.; Pfitzner, J.; Place, G. A. Design, synthesis, and 5-leukotriene-inhibiting properties of 1-thio-substituted butadienes. *J. Med. Chem.* **1990**, *33*, 1163–1170.
7. Holmeide, A. K.; Skattebøl, L. Syntheses of some polyunsaturated trifluoromethyl ketones as potensial phosholipase A_2 inhibitors. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 2271–2276.
8. Flock, S.; Lundquist, M.; Skattebøl, L. Syntheses of some polyunsaturated sulfur- and oxygen-containing fatty acids related to eicosapentaenoic and docosahexaenoic acids. *Acta Chem. Scand.* **1999**, *53*, 436–445.
9. Thommesen, T.; Sjursen, W.; Gåsvik, K.; Hanssen, W.; Brekke, O-L.; Skattebøl, L.; Holmeide, A. K.; Espevik, T.; Johansen, B.; Lægreid, A. J. Selective inhibitors of cytosolic or secretory phospholipase A_2, block TNF-induced activation of transcription factor nuclear factor-κB and expression of ICAM-1. *Immunology* **1998**, *161*, 3421–3430.
10. Ringbom, T.; Huss, U.; Stenholm, A.; Flock, S.; Skattebøl, L.; Perera, P.; Bohlin, L. Cox–2 inhibitory effects of naturally occurring and modified fatty acids. *J. Nat. Prod.* **2001**, *64*, 745–749.
11. Corey, E. J.; Fuchs, P. L. A synthetic method for formyl-ethynyl conversion. *Tetrahedron Lett.* **1972**, 3769–3772.
12. Brudermüller, M.; Musso, H. Synthesis of all-cis-1,4,7,10-cyclododecatetraene. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 298–299.
13. De la Rosa, M. A.; Velarde, E.; Guzman, A. Cross–coupling reactions of monosubstituted acetylenes and aryl halides catalyzed by palladium on charcoal. *Synth. Commun.* **1990**, *20*, 2059–2064.
14. Lawesson, S. O. A new method of preparing 2,4-dibromothiophene and its Grignard and lithium reagents. *Arkiv Kemi* **1957**, *11*, 317–324.
15. Johnson, A. L. Syntheses of the three isomeric ortho-substituted phenylthienyl benzoic acids. *J. Org. Chem.* **1976**, *41*, 1320–1324.