

An efficient stereoselective synthesis of a sulfur-bridged analogue of bosseopentaenoic acid as a potential antioxidant agent

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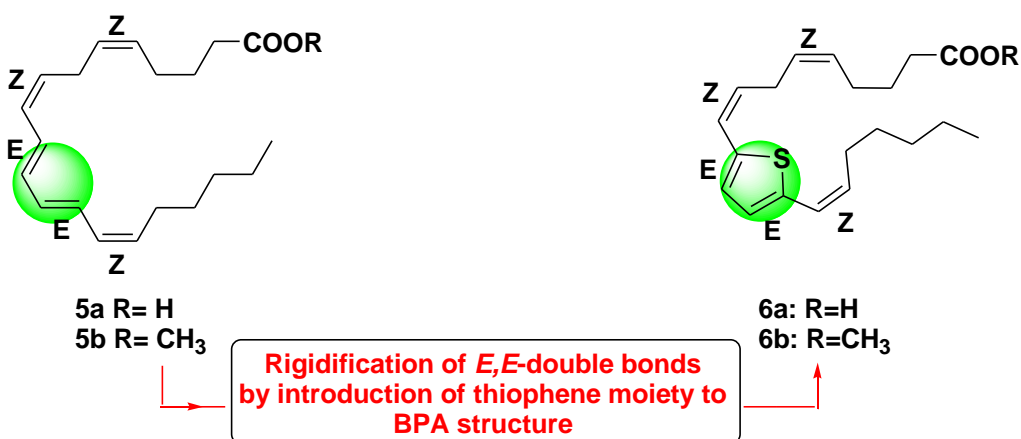
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Abstract

An efficient approach to the stereoselective synthesis of a novel sulfur-bridged analogue of bosseopentaenoic acid (BPA) by employing the Z-selective modified Boland semi-reduction procedure as the key step is described. The free radical scavenging potential of the thiophene analogue of bosseopentaenoic acid is studied. The results showed that the thiophene ring led to increased antioxidant activity.



Keywords: Bosseopentaenoic acid, sulfur-bridged, thiophene analogue, antioxidant activity

Introduction

Polyunsaturated fatty acids (PUFAs) are a class of compounds, which have gained interest due to an array of beneficial health effects as dietary supplements.¹⁻³ In physiological systems, ω -3 and ω -6 fatty acids, like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid, are mostly esterified to the phospholipid cell membrane.

Once PUFAs are released from the membrane they can participate in signal transduction, either directly or after enzymatic conversion to a variety of important, bioactive lipid mediators.⁴ In several studies the consumption of polyunsaturated fatty acids have shown positive health effects like reducing the risk of cardiovascular diseases^{5,6} and heart attack,⁷ positively associated with cognitive and behavioral performances^{4,5} as well as different types of cancer.^{6,7}

The promising biological effects as well as the complex chemical structures of the polyunsaturated fatty acids have made them interesting synthetic targets as well as lead compounds for medicinal chemists. Several attempts have been made to modify the PUFA structures, to improve or modify their biological activities, as well as to simplify the chemical synthesis. In 1985, Corey *et al.* substituted the methylene group at 7-position in arachidonic acid with sulfur.⁸ The resulting compound **1** possessed inhibitory activity for 5-lipoxygenase (5-LO). Later, Hanks *et al.* synthesized and tested for 5-LO inhibition several analogues of arachidonic acid containing a sulfur atom at the 5-position.⁹ Structure-activity studies suggested the sulfur atom preferably should be attached to *E*-alkene as in compound **2** which was the most active 5-LO inhibitor of those tested in this study. In 2007, Skattebøl *et al.*¹⁰ reported the synthesis of several thiophene-containing PUFAs such as compounds **3** and **4** (Figure 1).

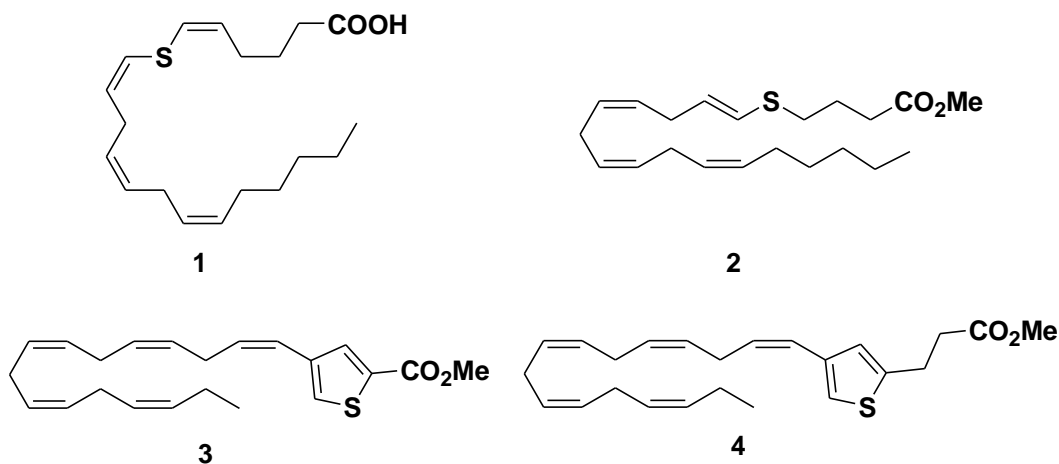


Figure 1. Chemical structures of biological active sulfur-containing PUFAs.

From the aforementioned results, it is worth noting that the introduction of sulfur-bridged atom to polyunsaturated fatty acids (PUFAs) is an approach which has received great interest in enhancement of biological effects. Hence, we envisaged to synthesize a rigidified analogue of bosseopentanoic acid **6a** by replacement the two conjugated *E,E*-double bonds existed in bosseopentanoic acid **5a** to thiophene moiety and testing their antioxidant activity (Figure 2).

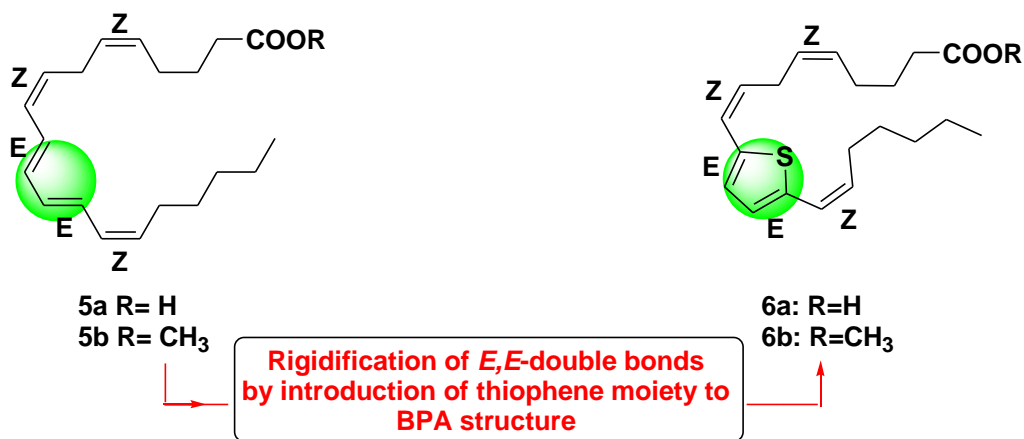


Figure 2. Chemical structure of bosseopentaenoic acid (BPA) **5a**, the thiophene analogue of BPA **6a** and the corresponding esters **5b** and **6b**.

Bosseopentaenoic acid (BPA) **5a** is a naturally occurring ω -6 fatty acid which containing four conjugated double bonds with *Z,E,E,Z*-configuration respectively and one skipped double bond with *Z*-configuration. The compound was isolated from the red alga *Bossiella orbigniana* by Burgess *et al.* in 1991,¹¹ and the first total synthesis of methyl bosseopentaenoate **5b** was published in 2011.¹² Herein, we report a synthetic strategy towards a thiophene analogue of BPA **6a** as well as its biological activity evaluation in comparison with BPA **5a**.

Results and Discussion

Chemistry

A retrosynthetic analysis of the polyunsaturated thiophene is outlined in Figure 3. The triyne **7** is the key intermediate in the synthesis of the target molecule **6a**. The compound **7** can be converted to **6a** by *Z*-stereoselective semi-reduction of the three triple bonds to corresponding three *cis*-double bonds followed by hydrolysis of ester group to acid. In the described retrosynthetic pathway, the commercially available 2-iodothiophene **11** was selected to be as starting material in the synthesis of thiophene analogue of bosseopentaenoic acid **6a** (Figure 3).

Our synthetic strategy started with the preparation of compound **13** from the reaction of 2-iodothiophene (**15**) with hept-1-yne (**14**) to produce compound **13** in 88% yield. This compound was reacted with lithium diisopropylamide (LDA) to form non-isolated intermediate 5-lithiothiophene¹³ **13'** that was subsequently reacted with iodine to form 2-(hept-1-yn-1-yl)-5-iodothiophene (**11**) in 53% yield. A Sonogashira coupling¹⁴ between compound **11** and propargyl alcohol **12** afforded compound **10** in 86% yield. Conversion of this alcohol **10** to corresponding bromide was performed using carbon tetrabromide and triphenyl phosphine at room temperature^{15,16} to obtain compound **8** in 77% yield. The ¹H NMR analysis of compound **8** showed a singlet at δ 4.39 ppm, characteristic for CH₂-Br. Triyne **7** was achieved in good yield (71%) through a skipped alkyne synthesis by coupling propargyl bromide **8** with methyl 5-hexynoate **9**.^{17,18} A *Z*-stereoselective semi-reduction of triyne **7**, was carried out *via* a modified Boland protocol using Zn(Cu/Ag) in presence of trimethylsilyl chloride (TMSCl)^{19,20} at room temperature, to produce compound **6b** in 65% yield. The modified Boland protocol, using Zn(Cu/Ag) in presence of TMSCl, proved to be important for this reaction^{12,20-23} (Scheme 1); the same reduction carried out with a Lindlar catalyst resulted in a complex mixture of products.²⁴

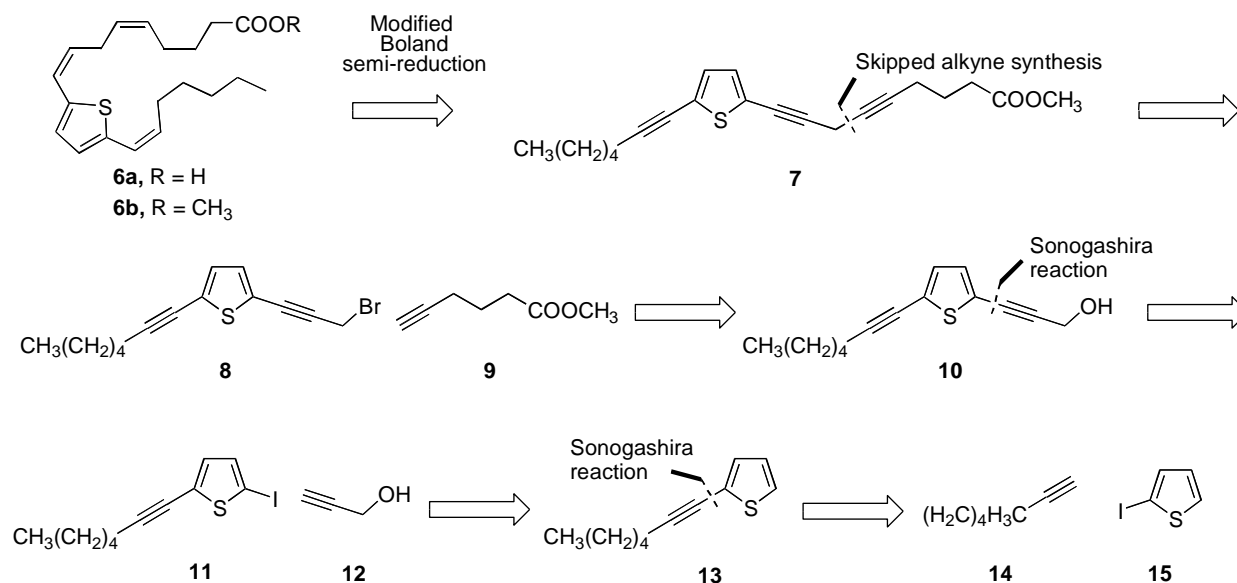
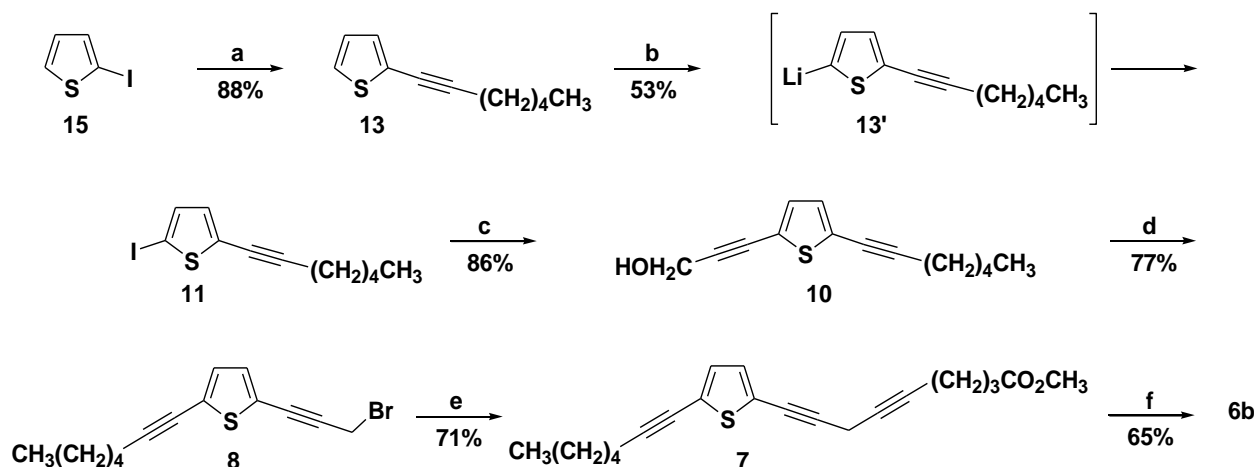


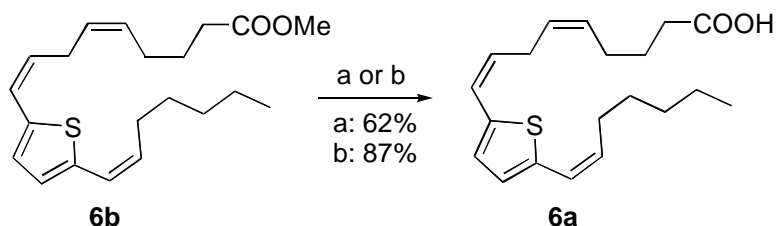
Figure 3. Retrosynthetic analysis of sulfur-bridged analogue of bosseopentaenoic acid **6a**.



Scheme 1. Reagents and reaction conditions: a) Pd(Ph₃P)₂Cl₂ (5 mol%) CuI (10 mol%), 1-heptyne (**14**), THF, room temperature; 3 h; b) LDA, I₂, THF, -40 °C, 1 h; c) Pd(Ph₃P)₂Cl₂ (5 mol%) CuI (10 mol%), propargyl alcohol (**12**), THF, room temperature, 3 h; d) CBr₄, PPh₃, CH₂Cl₂, room temperature, 2 h; e) Methyl hexynoate (**9**), CuI, *n*-Bu₄NBr, Na₂CO₃, DMF, room temperature, 16 h; f) Zn(Cu/Ag), TMSCl, (MeOH: H₂O, 1:1), room temperature, 6 h.

The hydrolysis of the methyl ester **6b** using LiOH, provided the corresponding acid **6a** in 62% isolated yield. An alternative milder and potentially higher yielding procedure for the hydrolysis of ester group existed in the sensitive substrate by the use of a lithium salt was considered.²⁵ However, in our case the reaction did not proceed when the ester **6b** was treated with 10 equivalents of LiI in THF/H₂O (3:1) at room temperature for 24 h. In addition, the use of triethylamine with LiI gave a low conversion to the carboxylic acid **6a**. From these results, we decided to investigate a mild and more efficient procedure for the hydrolysis of the methyl ester of the thiophene analogue **6b**, as well as methyl bosseopentaenoate **5b** that was prepared according to the reported literature procedures.¹² Herein, an *in situ* formation of LiI in a two-step reaction was carried out. The first step is the formation of TMSI by mixing TMSCl with KI. Then LiOH was added subsequently, to produce

lithium iodide (LiI) that mediated the hydrolysis of the methyl ester **6b** under mild and efficient conditions to afford acid **6a** after 6 hours in 87% isolated yield (Scheme 2).



Scheme 2. Reagents and reaction conditions: a) LiOH (6 eq), MeOH:H₂O:THF (2:2:1), 4 h. b) TMSCl (3 eq), KI (3 eq), LiOH (3 eq), MeOH:H₂O:THF (2:1:1), 6 h.

The correct configuration of the final compound was assigned by ¹H NMR and ¹³C NMR data. The purity of the thiophene analogue **6b** was determined by HPLC to be 99%. With this procedure, the hydrolysis of the ester group in methyl bosseopentaenoate **5b** was executed. This method provided bosseopentaenoic acid **5a** in 82% yield. The NMR data of BPA **5a** were in good agreement with those previously reported.¹¹

Biological evaluation

The free radical-scavenging potential of both BPA **5a** and the thiophene analogue **6a** was investigated in a DPPH scavenging assay in comparison with ascorbic acid as standard antioxidant agent. The thiophene analogue **6a** exhibited good radical scavenging activity with SC₅₀ 5.74 μM. However, bosseopentaenoic acid **5a** exhibited SC₅₀ 6.82 μM (Table 2).

Table 2. Biological evaluation of the antioxidant activity of thiophene analogue using a DPPH radical scavenging method

Compound	Antioxidant activity
	DPPH radical scavenging SC ₅₀ (μM) ^a
5a	6.82 ± 0.04
6a	5.74 ± 0.05
Ascorbic acid	9.34 ± 0.07

^a Results of three experiments performed in triplicate.

Based on these results, both BPA and thiophene analogue have effect in scavenging superoxide. However, the thiophene analogue **6a** has the higher susceptibility to oxidation more than BPA **5a** dependent on the presence of sulfur-bridged atom in the structure that increased the stability of compound **6a**.

Conclusions

An efficient stereoselective synthesis of a thiophene analogue of bosseopentaenoic acid **6a** was achieved in 12% yield over 7 steps, as well as antioxidant activity were evaluated. The the two *E,E*-double bonds in the

structure of bosseopentaenoic acid was replaced by thiophene moiety to act as a rigidified analogue of BPA. This replacement resulted in a less flexible structure with fewer rotational options. The key step in our synthetic approach was the Z-selective modified Boland-semi-reduction procedure to establish the three Z-double bonds in one reaction. The biological evaluation revealed the thiophene analogue **6a** exhibited an improved antioxidant activity compared to the lead bosseopentaenoic acid **5a**.

Experimental Section

General. All reagents and solvents were used as purchased without further purification. Analytical TLC was performed on silica gel 60 F254 Aluminium sheets (Merck). Flash column chromatography was performed on silica gel 60 (40-60 μm , Fluka). NMR spectra were recorded on a Bruker Avance DPX spectrometer at 300 or at 400 MHz for ^1H NMR, 75 or 101 MHz for ^{13}C NMR respectively. Coupling constants (J) are reported in hertz, and chemical shifts are reported in ppm (δ) relative to CDCl_3 (7.24 ppm for ^1H and 77.40 ppm for ^{13}C). The HPLC analyses were performed using a Agilent Technologies 1200 Series with an Eclipse XD 8-C18 5 μm , 4.6x150 mm column. High-resolution mass (ESI-MS) spectra were measured on (TOF) LC/MS; 6230 Series Accurate-Mass Time-of-Flight.

2-(hept-1-yn-1-yl)thiophene (13). To a mixture of $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (0.33 g, 0.48 mmol, 5 mol%) and CuI (0.18 g, 0.95 mmol, 10 mol%) in THF (5 mL) under nitrogen, piperidine (2.8 mL, 28.56 mmol, 3 eq) and 2-iodothiophene (15) (2 g, 9.52 mmol, 1 eq) were added, followed by the addition of 1-heptyne (14) (0.91 g, 9.52 mmol, 3 eq). The reaction mixture was allowed to stir for 3 h at room temperature. The resulting mixture was diluted with EtOAc (10 mL) then filtered through short pad of silica gel using EtOAc (30 mL) as eluent. The solution was washed with saturated ammonium chloride, dried (MgSO_4) and evaporated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, hexane/EtOAc, 90:10) to afford the title product as a colorless oil (1.49 g, 88%). ^1H NMR (300 MHz, CDCl_3): δ 7.20 (d, J 6.2 Hz, 1H), 7.04-6.91 (m, 2H), 2.44 (t, J 7.1, 2H), 1.61-1.58 (m, 2H), 1.33-1.25 (m, 4H), 0.87 (t, J 8.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 132.6, 131.4, 126.0, 125.3, 122.6, 95.8, 97.1, 31.5, 29.8, 22.5, 14.3. HRMS calcd. for $\text{C}_{11}\text{H}_{15}\text{S}$ $[\text{M}+\text{H}]^+$ 179.0850, found $[\text{M}+\text{H}]^+$ 179.0841.

2-(hept-1-yn-1-yl)-5-iodothiophene (11). A solution of lithium diisopropylamide (LDA) (1.0 M in THF/hexane, 0.71 mL, 7.09 mmol, 1.05 eq) in THF (20 mL) was cooled to $-40\text{ }^\circ\text{C}$ and 2-(hept-1-yn-1-yl)thiophene (13) (1.20 g, 6.74 mmol, 1 eq) was added with stirring. After 10 min the mixture was warmed to $-10\text{ }^\circ\text{C}$ and stirred for approximately 10 min. The mixture was re-cooled to $-40\text{ }^\circ\text{C}$ and iodine (1.80 g, 7.09 mmol, 1.05 eq) was added in one portion. The reaction mixture was allowed to stir for 1 h and then it was warmed slowly to $0\text{ }^\circ\text{C}$ and saturated NH_4Cl solution (5 mL) was added. After extraction with Et_2O , the combined extracts were dried with MgSO_4 and the solvent was evaporated. The resulting crude product was purified by column chromatography (silica gel, hexane) to afford the title product as a colorless oil (1.08 mg, 53%). ^1H NMR (300 MHz, CDCl_3): δ 7.05 (d, J 3.8 Hz, 1H), 6.94 (d, J 3.8 Hz, 1H), 2.40 (t, J 7.1 Hz, 2H), 1.58-1.56 (m, 2H), 1.39-1.27 (m, 4H), 0.89 (t, J 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 132.5, 131.0, 126.4, 122.5, 96.3, 73.6, 31.5, 28.5, 22.5, 20.1, 14.3. HRMS calcd. for $\text{C}_{11}\text{H}_{14}\text{SI}$ $[\text{M}+\text{H}]^+$ 304.9860, found $[\text{M}+\text{H}]^+$ 305.1094.

3-(5-(Hept-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-ol (10). To a mixture of $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (103 mg, 0.17 mmol, 5 mol%) and CuI (57 mg, 0.33 mmol, 10 mol%) in THF (5 mL) under nitrogen, piperidine (0.875 mL, 9.87 mmol, 3 eq) and 2-(hept-1-yn-1-yl)-5-iodothiophene (11) (1.0 g, 3.29 mmol, 1 eq) were added, followed by the addition

of propargyl alcohol (12) (497 mg, 3.29 mmol, 1 eq). The reaction mixture was allowed to stir for 3 h at room temperature. The resulting mixture was diluted with EtOAc (10 mL) then filtered through short pad of silica gel using EtOAc (30 mL) as eluent. The solution was washed with saturated ammonium chloride, dried (MgSO_4) and evaporated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, hexane/EtOAc, 90:10) to afford the title product as a colorless oil (1.5 g, 86%). ^1H NMR (300 MHz, CDCl_3): δ 7.01 (d, J 3.8 Hz, 1H), 6.89 (d, J 3.8 Hz, 1H), 4.49 (s, 2H), 2.42 (t, J 7.1 Hz, 2H), 1.59-1.56 (m, 2H), 1.44-1.23 (m, 4H), 0.89 (t, J 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 132.5, 131.1, 126.4, 122.5, 96.2, 91.6, 79.2, 73.6, 52.1, 31.4, 28.5, 22.6, 20.1, 14.3. HRMS calcd. for $\text{C}_{14}\text{H}_{17}\text{OS}$ $[\text{M}+\text{H}]^+$ 233.1000, found $[\text{M}+\text{H}]^+$ 233.0897.

2-(3-bromoprop-1-yn-1-yl)-5-(hept-1-yn-1-yl)thiophene (8). To a stirred solution of 3-(5-(hept-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-ol (10) (1 g, 4.31 mmol) and CBr_4 (1.57 g, 4.74 mmol) in dichloromethane (30 mL) at 0 °C, Ph_3P (1.36 g, 5.17 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum to obtain a brown oil and quickly added to hexane with stirring (100 mL). The triphenylphosphine oxide (Ph_3PO) was formed as a white precipitate and filtered off. The filtered solution was concentrated under reduced pressure using a rotary evaporator and then purified by flash column chromatography (silica gel, hexane) yielding compound 8 as colorless oil (0.98 g, 77%). ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.01 (s, 2H), 4.39 (s, 2H), 2.39 (t, J 7.4 Hz, 2H), 1.59-1.56 (m, 2H), 1.44-1.23 (m, 4H), 0.89 (t, J 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 132.5, 131.0, 126.4, 122.5, 96.3, 91.6, 79.2, 73.6, 47.1, 31.5, 28.5, 22.5, 20.0, 14.3. HRMS calcd. for $\text{C}_{14}\text{H}_{16}\text{BrS}$ $[\text{M}+\text{H}]^+$ 295.0156 found $[\text{M}+\text{H}]^+$ 295.0152.

Methyl-9-(5-(hept-1-yn-1-yl)thiophen-2-yl)nona-5,8-diynoate (7). To a mixture of Na_2CO_3 (0.36 g, 3.38 mmol, 1.5 eq), CuI (0.43 g, 2.26 mmol, 1 eq), $n\text{-Bu}_4\text{NBr}$ (0.18 g, 0.68 mmol, 0.3 eq) in DMF (10 mL) at -20 °C, 5-methyl hexynoate (9) (0.28 g, 2.26 mmol, 1 eq) was added, followed by addition of propargyl bromide 8 (0.80 g, 2.71 mmol, 1.2 eq). The reaction was allowed to stir at room temperature overnight. Et_2O (5 mL) was added, and the resulted precipitate was filtered through a short pad of silica gel. Water (10 mL) was added to form an aqueous layer which was extracted with Et_2O (3 x 25 mL). The organic layer was washed with saturated ammonium chloride and dried over MgSO_4 . The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/EtOAc, 95:5). The title compound was isolated as colorless oil, which soon turned to yellow, in 71% yield (0.65 g). ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.00 (s, 2H), 3.62 (s, 3H), 2.95 (t, J 6.2 Hz, 2H), 2.42 (t, J 7.4 Hz, 2H), 2.38 (t, J 7.4 Hz, 2H), 2.31-2.13 (m, 2H), 1.69-1.26 (m, 6H), 1.58-1.56 (m, 2H), 0.87 (t, J 7.4 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): 176.4, 132.8, 131.6, 130.4, 129.6, 129.3, 129.0, 128.9, 128.7, 128.0, 126.8, 105.4, 100.8, 95.4, 85.2, 84.6, 80.0, 52.1, 33.2, 31.5, 28.5, 24.2, 22.5, 20.1, 18.6, 14.3, 11.2. HRMS calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 341.1475 found $[\text{M}+\text{H}]^+$ 341.1542.

Methyl-(5Z,8Z)-9-(5-((Z)-hept-1-en-1-yl)thiophen-2-yl)nona-5,8-dienoate (6b). For Z-selective semi-reduction of the triyne 7 we used the modified Boland procedure.¹² The $\text{Zn}(\text{Cu}/\text{Ag})$ was prepared according to reported procedure in literature.¹⁹ To a suspension of the $\text{Zn}(\text{Cu}/\text{Ag})$ (2.0 g) in $\text{MeOH}:\text{H}_2\text{O}$ (1:1, 6 mL), the triyne 7 (0.40 g, 0.08 mmol) was added and followed subsequently by the addition of trimethylsilyl chloride (TMSCl) (0.1 mL, 0.80 mmol). The reaction mixture was stirred at ambient temperature for 6 h. Upon completion Et_2O (5 mL) was added, the reaction mixture was filtered through a short plug of silica gel, and eluted with Et_2O (3 x 5 mL). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), the organic layer was separated, dried (MgSO_4), and then removal of the solvent afforded a residue that was purified by column chromatography (silica gel, hexane:EtOAc, 8:2, 7:3, 6:4, 1:1) to afford the desired triene 6b in 65% yield (0.26 g). ^1H NMR (300 MHz, CDCl_3): δ 7.05 (s, 2H), 6.11-5.95 (m, 2H), 5.46-5.27 (m, 4H), 3.65 (s, 3H), 2.91 (t, J 6.2 Hz, 2H), 2.22 (t, J 7.4 Hz, 2H), 2.13-2.05 (m, 4H), 1.65 (p, J 7.4 Hz, 2H), 1.23-1.20 (m, 6H), 0.86 (t, J 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 174.0, 142.2, 139.4, 131.4, 129.6, 129.3, 129.0, 128.9, 125.2,

123.7, 122.1, 51.8, 33.8, 31.8, 29.7, 28.3, 26.9, 26.6, 25.1, 22.9, 14.4. HRMS calcd. for $C_{21}H_{31}O_2S$ $[M+H]^+$ 347.2045, found $[M+H]^+$ 347.2187.

(5Z,8Z)-9-(5-((Z)-hept-1-en-1-yl)thiophen-2-yl)nona-5,8-dienoic acid (6a)

Procedure A. The methyl ester 6b (0.10 g, 0.29 mmol, 1 eq.) dissolved in THF (1 mL) was transferred to the reaction flask contained MeOH:H₂O (2:1, 3 mL). Solid lithium hydroxide monohydrate (73 mg, 1.74 mmol, 6 eq.) was added to the reaction mixture at 0 °C and it was stirred at 0 °C for 30 min., before the mixture was warmed to room temperature and it was allowed to stir for additional 3 h. The reaction mixture was acidified with saturated aq. NaH₂PO₄ (2 mL). EtOAc (5 mL) was added and the organic layer was separated. The aqueous layer was followed subsequently by extraction with EtOAc (2 × 5 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 7:3, 6:4, 1:1, 3:7, 2:8) to afford thiophene analogue of bosseopentaenoic acid 6a in 62% yield (59 mg).

Procedure B. A solution of trimethylsilyl chloride (TMSCl) (0.11 g, 0.87 mmol, 3 eq), Potassium iodide (KI) (0.14 g, 0.87 mmol, 3 eq) in MeOH:H₂O (2:1, mL) was stirred at room temperature. After 15 min solid lithium hydroxide monohydrate (12 mg, 0.29 mmol, 3 eq) dissolved in H₂O (1 mL) was added slowly, and the reaction mixture was stirred for additional 30 min. The methyl ester 6b (0.1 g, 0.29 mmol) dissolved in THF (1 mL) was added and the resulting mixture was stirred at ambient temperature for 6 h. Upon completion 1M Na₂HPO₄ (2 mL) and EtOAc (2 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 7:3, 6:4, 1:1, 3:7, 2:8) to obtain thiophene analogue of bosseopentaenoic acid 6a in 87% yield (83 mg). ¹H NMR (300 MHz, CDCl₃): δ 12.51 (s, 1H), 7.02 (s, 2H), 6.02-5.97 (m, 2H), 5.48-5.30 (m, 4H), 2.89 (t, *J* 6.2 Hz), 2.16 (t, *J* 7.5 Hz, 2H), 2.16 (t, *J* 7.5 Hz, 2H), 2.11-2.05 (m, 2H), 1.66 (p, *J* 7.5 Hz, 2H), 1.32-1.20 (m, 6H), 0.88 (t, *J* 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 180.1, 142.3, 139.4, 131.5 (2 × C), 129.7, 129.4, 129.1, 128.9, 123.3, 122.0, 33.8, 31.9, 29.7, 28.3, 26.9, 26.6, 25.2, 22.9, 14.4. HRMS calcd. for $C_{20}H_{28}O_2S$ $[M-H]^+$ 331.1732, found $[M-H]^+$ 331.1842. Purity (HPLC) 99%.

Bosseopentaenoic acid (5a). A solution of TMSCl (31 mg, 0.29 mmol, 3 eq), KI (48 mg, 0.29 mmol, 3 eq) in MeOH:H₂O (2:1, 3 mL) was allowed to stir at room temperature. After 15 min solid lithium hydroxide monohydrate (12 mg, 0.29 mmol, 3 eq) dissolved in H₂O (1 mL) was added slowly, and the reaction mixture was stirred for additional 30 min. The methyl bosseopentaenoate 5b (30 mg, 0.096 mmol) dissolved in THF (1 mL) was added and the resulting mixture was stirred at ambient temperature for 6 h. Upon completion 1M Na₂HPO₄ (2 mL) and EtOAc (2 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, hexane: EtOAc, 7:3, 6:4, 1:1, 3:7, 2:8) to obtain bosseopentaenoic acid 5a in 82% yield (24 mg). Spectroscopic and physical data were in agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃): δ 6.49 (dd, *J* 13.4, 10.8 Hz, 2H), 6.16-6.42 (m, 2H), 5.25-5.48 (m, 4H), 2.89 (t, *J* 7.4 Hz, 2H), 2.13 (q, *J* 7.4 Hz, 2H), 2.05 (t, *J* 7.4 Hz, 2H), 1.54 (p, *J* 7.4 Hz, 2H), 1.21-1.91 (m, 6H), 0.88 (t, *J* 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 180.0, 133.6, 133.0, 132.1, 129.9, 129.2, 129.0, 128.6, 128.4, 127.0, 126.5, 32.8, 31.3, 29.0, 27.9, 26.3, 26.2, 24.3, 22.6, 13.9. HRMS calcd. for $C_{20}H_{30}O_2$ $[M+Na]^+$ 325.2099, found $[M+Na]^+$ 325.2038. Purity (HPLC) 98%. The NMR spectra was consistent with the published data.¹¹

Antioxidant activity DPPH scavenging assay

To investigate the antioxidant activity an 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay was used. Various concentrations of the compounds (0.1-50 µg/mL) were prepared in MeOH. The solution (1.0 mL) was

added to 1.0 mL (0.2 mg/mL) methanol solution of DPPH and kept in dark. The decrease in absorbance at 517 nm was observed after 30 min. The percentage scavenging of radical was determined and the results were expressed as the concentration of sample where absorbance of DPPH decreases 50% (SC₅₀ values, μ M).²⁶

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