# Two novel racemic synthetic approaches to $LTB_4$ and $LTB_3$ methyl esters

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The formal racemic synthesis of $LTB_4$ and $LTB_3$ methyl esters **1** and **2** is reported by introducing in a one step-procedure the *E*,*E*,*Z*-conjugated trienic system provided by (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **3** and (1*E*,3*E*,5*Z*)-1-bromo-7,7-diethoxyhepta-1,3,5-triene **4**, respectively, as building blocks.

## Introduction

Leukotriene $B_4$ ($LTB_4$) (Fig. 1), an important metabolite of arachidonic acid,[1] biosynthesised *via* the 5-lipoxygenase pathway,[2] is one of the most potent inducers of chemotaxis, chemokinesis, aggregation and degranulation of leukocytes. Important roles in allergic,[3a] inflammatory[4] and immunological reaction[5] have been attributed to $LTB_4$. On the other hand, following an analogous 5-lipoxygenase pathway, eicosa-5,8,11-trienoic acid is metabolised *in vivo* into $LTB_3$.[6] The latter has also been reported to possess biological activities, similar to $LTB_4$.[7]

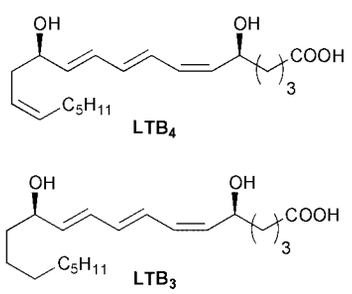
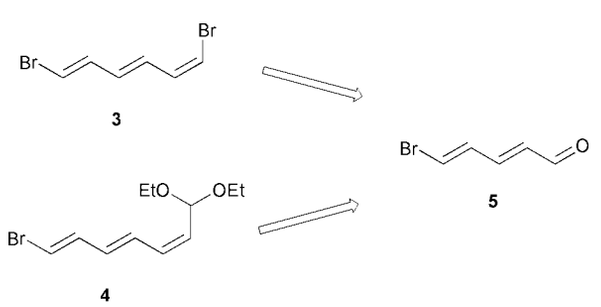



**Fig. 1**

As a result of their physiological importance and limited availability from biological sources, a number of synthetic routes to $LTB_4$[8] and to $LTB_3$[8d,8h,9] have been described in the literature.

Herein, we report two new synthetic approaches to $LTB_4$ and $LTB_3$ as their methyl esters **1** and **2** based on the great reactivity and versatility of our reagent (2*E*,4*E*)-5-bromopenta-2,4-dienal **5** (Scheme 1).[10] Thus, as summarised in Scheme 1, it can be




**Scheme 1**

successfully used to yield diastereomerically pure (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene[10a] **3** and (1*E*,3*E*,5*Z*)-1-bromo-7,7-diethoxyhepta-1,3,5-triene[11] **4** (Scheme 1), following methodologies successfully developed in our group.[10a,11]

One observes that, as in the target leukotrienes, the trienic *E*,*E*,*Z*-conjugated system already exists in compounds **3** and **4**; hence, they could be *a priori* seen as building blocks able to give access to the title methyl esters **1** and **2**.

To the best of our knowledge, the syntheses of $LTB_4$ and $LTB_3$ by a stereocontrolled introduction of the *E*,*E*,*Z* conjugated trienic unit, in a one step procedure, have not been reported so far.

## Results and discussion

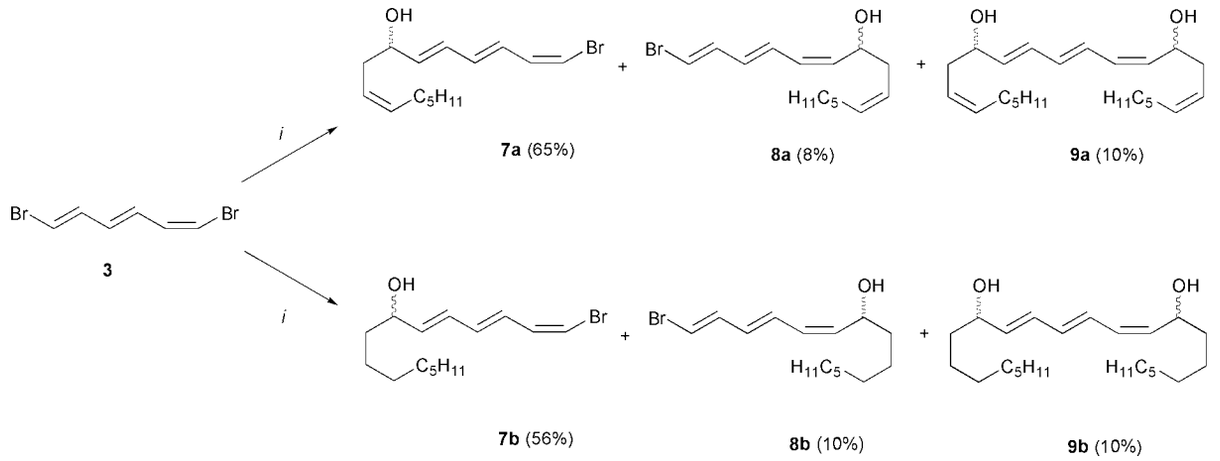
Two synthetic strategies were imagined, based mainly on the ability of the proposed starting materials **3**[10a,12] and **4**[11] to afford lithio derivatives by stereocontrolled halogen–metal exchange reactions and subsequent treatment with an appropriate aldehyde.

### Synthesis from (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene 3

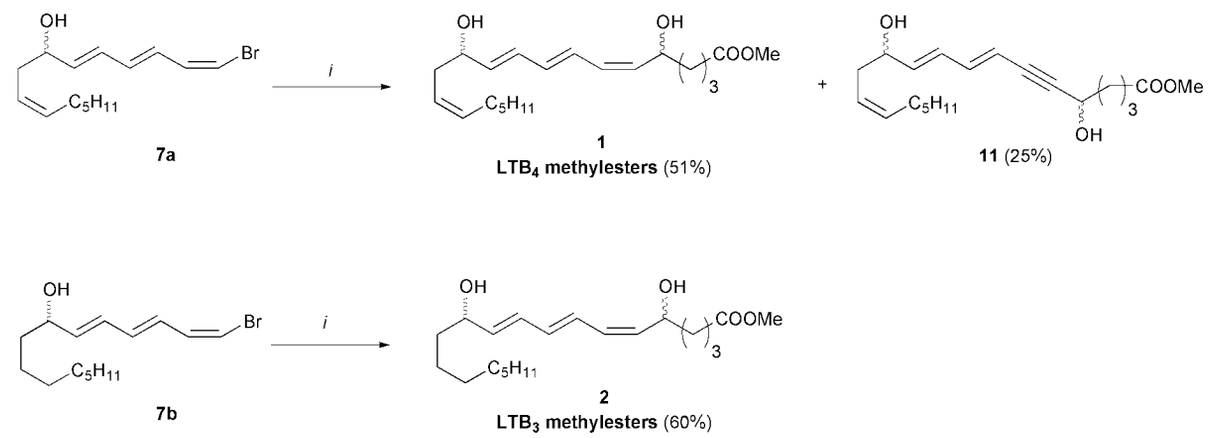
The 1*E*,3*E*,5*Z*-isomer of 1,6-dibromohexa-1,3,5-triene **3** has been previously prepared by us,[10a] exploiting a Wittig reaction performed on (2*E*,4*E*)-5-bromopenta-2,4-dienal[10] **5**.

Moreover, we have previously demonstrated that the two bromine atoms linked at C-1, C-6 significantly exhibit different reactivity when **3** is involved in a halogen–metal exchange reaction[10a] or in a palladium-catalyzed cross-coupling process.[13] This behaviour was considered of crucial importance since simple retrosynthetic disconnection revealed the availability of $LTB_4$ and $LTB_3$ from a 1*E*,3*E*,5*Z*-hexatriene dianion equivalent in reaction with two different aldehydes. Thus, the synthetic approaches to $LTB_4$ and $LTB_3$ methyl esters **1** and **2** were attempted as two successive selective bromine–lithium exchange reactions, followed by quenching of the reaction mixture with the required aldehyde (Scheme 2).

Indeed, a first bromine–lithium exchange reaction on pure 1*E*,3*E*,5*Z*-isomer **3**, by treatment with *tert*-butyllithium in diethyl ether at −75 °C, occurred with high selectivity on the bromine atom of the *E* double bond. The condensation with (3*Z*)-non-3-enal **6a** (synthetic approach to $LTB_4$ methyl esters **1**) or nonanal **6b** (synthetic approach to $LTB_3$ methyl esters **2**), afforded the desired monosubstituted compounds **7a** and **7b** in large excess over the side products **8a**, **9a** and **8b**, **9b**, respectively. After optimisation of the reaction conditions and column chromatography, the expected monobrominated derivatives **7a** and **7b** and the by-products **8a**, **9a** and **8b**, **9b** were isolated pure in the molar proportions **7a** : **8a** : **9a** 65 : 8 : 10 and **7b** : **8b** : **9b**




**Scheme 2** *Reagents and conditions*: *i*, Bu$^t$Li, $Et_2O$, −75 °C, 90 min; (3*Z*)-non-3-enal **6a** or nonanal **6b**, 0 °C, 90 min.




**Scheme 3** *Reagents and conditions*: *i*, Bu$^t$Li, $Et_2O$, −75 °C, 90 min; methyl 4-formylbutanoate **10**, 0 °C, 60 min.

56 : 10 : 10 (Scheme 2) and fully characterised. Discrimination between pure diastereomeric bromohydrins **7a** *vs.* **8a** and **7b** *vs.* **8b** and stereochemical analyses of all new compounds **7**–**9** were made by using $^1$H NMR spectroscopy. The stereochemistry of the trienic system of compounds **7**–**9** has been determined from the *J* values of the different double bonds (for example, compound **7a**: $J_{1,2}$ = 7.1; $J_{3,4}$ = 13.5 and $J_{5,6}$ = 13.8 Hz). All compounds **7**–**9** were obtained from the starting material **3** with total retention of configuration.

Finally, we note that (3*Z*)-non-3-enal **6a** was prepared in 91% yield by oxidation of the corresponding commercially available (3*Z*)-non-3-en-1-ol by using the Dess–Martin procedure.[14]

Keeping in mind that the bromohydrins **7a**,**b** are useful intermediates in the syntheses of $LTB_4$ and $LTB_3$ methyl esters **1** and **2**, respectively, the next step of the chemistry was straightforward. Thus, a second bromine–lithium exchange reaction was performed on pure isolated **7a**,**b** followed by quenching with methyl-4-formylbutanoate[15] **10** (Scheme 3).

The $LTB_4$ methyl esters **1** (as a non-separable diastereomeric mixture) were obtained and isolated in analytical purity after column chromatography in 51% yield (with respect to **7a**, overall yield 33% *vs.* starting material **3**). We mention, however, the occurrence of the side acetylenic product **11**, in 25% yield (from **7a**), presumably as the result of the dehydrobromination of **7a** promoted by the Bu$^t$Li. This compound **11** has been isolated pure and fully analyzed.

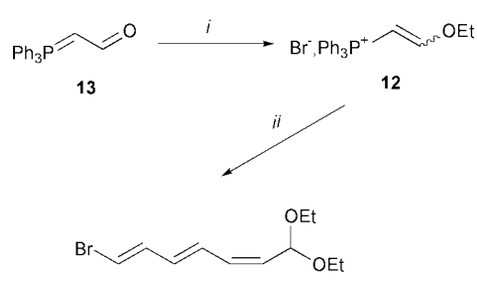
Similar methodology carried out with **7b** afforded the $LTB_3$ methyl esters **2** (as a non-separable diastereomeric mixture) in 60% yield (overall yield 34% with respect to **3**).

The isolated pure $LTB_4$ and $LTB_3$ methyl esters **1** and **2** have been fully characterised using classical methods.

In our opinion, the above results reveal a simple and convenient route towards $LTB_4$ and $LTB_3$ precursors in a two-step procedure from the readily available (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **3**.

## Synthesis *via* (1*E*,3*E*,5*Z*)-bromo-7,7-diethoxyhepta-1,3,5-triene **4**

In this second synthetic strategy, the starting material was (2*E*,4*E*)-5-bromopenta-2,4-dienal[10] **5** (Schemes 1 and 4). As the chemistry depicted in Scheme 4 suggests, the crucial step should be the Wittig homologation of aldehyde **5** promoted by the diethyl acetal of **13**. Then, in order to prepare the diethoxy derivative **4**, the early stage of our research was inspired by the work of Bestmann[16] concerning the diastereoselective synthesis of α,β-unsaturated aldehydes with high *Z* stereocontrol. However, in order to optimise the formation of **4**, we had to modify Bestmann's experimental protocol[16] (Scheme 4).




**Scheme 4** *Reagents and conditions*: *i*, EtBr, reflux, 2 days; *ii*, **5**, EtONa, THF, −10 °C, reflux, 12 h.

Surprisingly, we note that attempts at condensing directly the aldehyde **5** with the diethyl acetal of **13** (prepared from **12** and EtONa) failed since non-reproducible results were obtained. To ensure the accurate formation of **4**, we had to introduce the

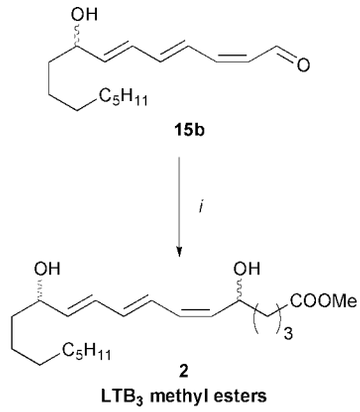
non-enolisable aldehyde **5** to the reaction mixture containing the phosphonium salt **12** prior to EtONa. The addition of the latter generated *in situ* the diethyl acetal of **13**, which condensed with **5**, as soon as it had formed. Thus, the aldehyde **5** added to the phosphonium enol ether salt **12** (available from the Trippett and Walker[17] phosphorylide reagent **13**), followed by sodium etharolate (EtONa), afforded the new ω-bromo conjugated trienic diethyl acetal **4** in 70% yield (with respect to **5**). The total 1*E*,3*E*,5*Z* stereochemistry of the latter, seen as the key intermediate, was revealed by means of $^1$H NMR spectroscopy.

Next, according to a bromine–lithium exchange reaction (treatment with Bu$^t$Li in $Et_2O$ at −75 °C) performed on pure isolated compound **4** followed by quenching with (3*Z*)-non-3-enal **6a** or nonanal **6b**, the desired hydroxytrienic diethyl acetals **14a**,**b** were obtained in 76 and 78% yield (from **4**), after column chromatographic purification, with total retention of configuration (Scheme 5).

Hydrolysis of **14a**,**b** under mild acidic conditions yielded the corresponding crude aldehydes **15a**,**b** in (almost) quantitative yield (Scheme 5). The unstable compounds **15a**,**b** (isomerisation into the corresponding conjugated aldehydes with an all *E* configuration) have been used as crude product.

Finally, an ω-butanoate homologation was performed on the aldehyde **15b** by using trimethyl 4-lithioorthobutanoate,[18] to afford the $LTB_3$ methyl esters **2** in 52% yield (from **15b**) after mild acidic hydrolysis (Scheme 6).

A similar procedure was previously reported by Taylor[8k] for the synthesis of $LTB_4$ methyl esters **1** by condensation of the same reagent with a silylated trienic aldehyde analogous to our precursor **15a**.




**Scheme 6** *Reagents and conditions*: *i*, $Li(CH_2)_3C(OMe)_3$, $Et_2O$, 0 °C, 120 min.

### Conclusions

In conclusion, we have succeeded in developing two new formal synthetic approaches to $LTB_4$ and $LTB_3$ methyl esters **1** and **2** by introduction of the conjugated trenic system in a one-step *E*,*E*,*Z*-stereocontrolled pathway.

From (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene **3** the $LTB_4$ and $LTB_3$ methyl esters **1** and **2** were obtained in two steps (in 33 and 34% overall yield respectively, *vs.* **3**) and from (2*E*,4*E*)-5-bromopenta-2,4-dienal **5** *via* the new reagent (1*E*,3*E*,5*Z*)-1-bromo-7,7-diethoxyhepta-1,3,5-triene **4**, the $LTB_3$ methyl esters **2** were obtained in four steps (overall yield 28% *vs*. **5**).

These new processes should be easily applicable to the synthesis of a wide variety of structural analogs. The synthesis with stereocontrol of the hydroxyallylic chiral centres is under investigation.

## Experimental

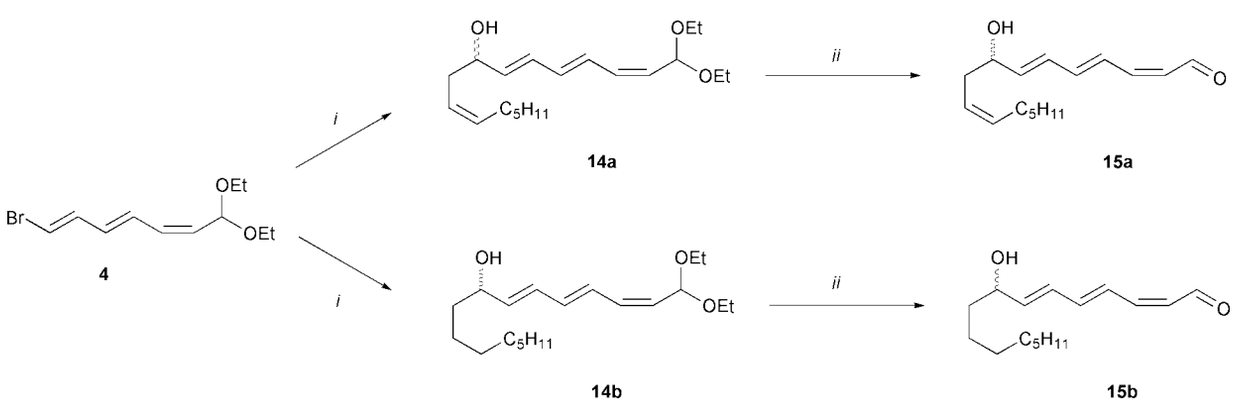
### General

IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer for samples as thin films. NMR spectra were recorded on a Bruker AC 200 MHz, Bruker Avance DPX 300 MHz, or Bruker AM 400 MHz with Aspect 3000 calculator. $CDCl_3$ or $C_6D_6$ was used as solvent. No $SiMe_4$ was added; rather, shifts were referenced to the solvent line (chemical shifts $\delta$ in ppm and coupling constants $J$ in Hz). Mass spectra were performed on an ATI-Unicam Automass apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min$^{-1}$), or on a JEOL JMS AX-500 spectrometer. Analytical TLC was performed on Kieselgel 60F-254–0.25 mm plates and developed with UV (250 nm) or phosphomolybdic acid. Products were purified by silica gel column chromatography (SDS Company, 230–400 mesh). All reactions were carried out under dry Ar. Microanalyses were carried out in IRCOF Microanalysis Laboratory of Rouen. Melting points were measured on a Reichert-Jung microscope apparatus. Solvents were purified according to standard procedures.

### (1*Z*,3*E*,5*E*,9*Z*)-1-Bromo-7-hydroxy-pentadeca-1,3,5,9-tetraene 7a

To a solution of (1*E*,3*E*,5*Z*)-1,6-dibromohexa-1,3,5-triene[10a,b] **3** (0.240 g, 1.00 mmol) in dry $Et_2O$ (4 mL), cooled to −75 °C, under argon was added a solution of Bu$^t$Li (1.07 mL of a 1.7 M solution in pentane; 1.80 mmol) slowly with a syringe. The reaction mixture was stirred for 90 min and a solution of (3*Z*)-non-3-enal[8j] **6a** (0.140 g, 1.00 mmol) in dry $Et_2O$ (1 mL) was introduced. The reaction mixture was warmed to 0 °C and was stirred for 90 min before treatment with water (2 mL). After extraction with $Et_2O$ (3 × 30 mL), the organic layer was dried ($MgSO_4$) and concentrated. By silica gel column chromatography [pentane–$Et_2O$ (80 : 20 v/v)] we isolated and identified the expected monosubstituted compound **7a** (0.195 g, 65%) as a yellow oil, compound **8a** (0.025 g, 8%, yellow oil) and compound **9a** (0.035 g, 10%, yellow oil).

**Compound 7a.** $\nu_{max}$/cm$^{-1}$ 3114, 3050, 2976, 1630, 1487, 1047 and 688; $\delta_H$(300 MHz; $C_6D_6$) 0.86 (3H, t, *J* 6.7, 15-$H_3$), 1.15–




**Scheme 5** *Reagents and conditions*: *i*, Bu$^t$Li, $Et_2$, −75 °C, 90 min; (3*Z*)-non-3-enal **6a** or nonanal **6b**, 0 °C, 2h; *ii*, PTSA, acetone, water, 0 °C, 45 min.

1.35 (6H, m, 12–14-$H_2$), 2.00 (2H, m, 11-$H_2$), 2.28 (2H, m, 8-$H_2$), 4.00 (1H, q, *J* 6.4 and 7.0, 7-H), 5.30–5.45 (2H, m, 9-H and 10-H), 5.60 (1H, dd, *J* 6.4 and 13.8, 6-H), 5.80 (1H, d, *J* 7.1, 1-H), 6.10 (2H, m, 4-H and 5-H), 6.25 (1H, dd, *J* 7.1 and 10.4, 2-H) and 6.60 (1H, dd, *J* 10.4 and 13.5, 3-H); $\delta_C$(75 MHz; $C_6D_6$) 14.62 (C-15), 23.26 (C-14), 28.06 (C-11), 29.97 (C-12), 32.11 (C-13), 35.87 (C-8), 72.07 (C-7), 108.42 (C-1), 124.90 (C-9), 128.14 (C-3), 132.80 (C-4), 133.23 (C-2), 135.03 (C-10), 135.18 (C-5) and 139.07 (C-6) (Found: C, 60.38; H, 7.59. $C_{15}H_{23}BrO$ requires C, 60.21; H, 7.75%).

**(1*E*,3*E*,5*Z*,9*Z*)-1-Bromo-7-hydroxypentadeca-1,3,5,9-tetraene 8a.** $\nu_{max}$/cm$^{-1}$ 3134, 3060, 2985, 1630, 1055 and 670; $\delta_H$(300 MHz; $C_6D_6$) 0.80 (3H, t, *J* 6.7, 15-H), 1.10–1.40 (6H, m, 12–14-$H_2$), 2.00 (2H, m, 11-$H_2$), 2.40 (2H, m, 8-$H_2$), 4.40 (1H, m, 7-H), 5.30–5.50 (4H, m, 5–6-H and 9–10-H), 5.62 (1H, m, 3-H), 5.78 (1H, d, *J* 13.6, 1-H), 6.30 (1H, dd, *J* 11.7 and 15.1, 4-H) and 6.52 (1H, dd, *J* 10.9 and 13.6, 2-H); $\delta_C$(75 MHz; $C_6D_6$) 14.23 (C-15), 21.00 (C-14), 27.72 (C-11), 28.64 (C-12), 31.89 (C-13), 35.66 (C-8), 67.93 (C-7), 109.65 (C-1), 124.79 (C-9), 128.88 (C-5), 129.07 (C-4), 131.23 (C-2), 135.38 (C-10), 135.90 (C-3) and 137.72 (C-6) (Found: C, 60.38; H, 7.59. $C_{15}H_{23}BrO$ requires C, 60.21; H, 7.75%).

**(6*Z*,10*E*,12*E*,14*Z*,18*Z*)-9,16-Dihydroxytetraeicosa-6,10,12, 14,18-pentane 9a.** $\nu_{max}$/cm$^{-1}$ 3346, 2920, 1654, 1466 and 1032; $\delta_H$(300 MHz; $C_6D_6$) 0.88 (6H, m, 1-$H_3$ and 24-$H_3$), 1.15–1.34 (12H, m, 2–4-$H_2$, 21–23-$H_2$), 2.00 (4H, m, 5-$H_2$ and 20-$H_2$), 2.30 (4H, m, 8-$H_2$ and 17-$H_2$), 4.10 (1H, m, 9-H), 4.53 (1H, m, 16-H), 5.36–5.60 (5H, m, 6–7-H, 15-H and 18–19-H), 5.67 (1H, dd, *J* 5.9 and 15.0, 10-H), 6.02 (1H, t, *J* 11.5, 14-H), 6.14 (1H, dd, *J* 10.8 and 14.7, 12-H), 6.31 (1H, dd, *J* 10.8 and 15.0, 11-H) and 6.55 (1H, dd, *J* 11.5 and 14.7, 13-H); $\delta_C$(75 MHz; $C_6D_6$) 14.46 (C-1 and C-24), 23.12, 29.86, 31.99 (C-2–4 and C-21–23), 27.94 (C-5 or C-20), 27.96 (C-20 or C-5), 36.07 (C-17 or C-8), 36.19 (C-8 or C-17), 68.15 (C-16), 72.20 (C-9), 125.25, 125.28, 133.25, 133.36, 134.73 (C-6–7, C-15 and C-18–19) 128.31 (C-13), 130.03 (C-14), 130.42 (C-11), 134.38 (C-12) and 137.70 (C-10); *m*/*z* (CI, $CH_4$) 389 ($M^+$ + 29.1 %), 361 ($M^+$ + 1, 3), 343 (100), 325 (32), 249 (80), 231 (60), 189 (60), 137 (23) and 69 (28).

**(1*Z*,3*E*,5*E*)-1-Bromo-7-hydroxypentadeca-1,3,5-triene 7b**

According to the procedure described for preparation of compound **7a**, from (1*E*,3*E*,5*Z*)-1,6-dibromo-1,3,5-triene[10a,b] **3** (0.240 g, 1.00 mmol) and using a solution of nonanal **6b** (0.140 g, 1.00 mmol) in dry $Et_2O$ (1 mL) we isolated and identified, after silica gel column chromatography [pentane–$Et_2O$ (80 : 20 v/v)], compound **7b** (0.170 g, 56%) as a yellow solid, compound **8b** (0.030 g, 10%, yellow oil) and compound **9b** (0.035 g, 10%, yellow oil).

**Compound 7b.** Mp 32–33 °C; $\nu_{max}$/cm$^{-1}$ 3184, 3060, 2968, 1650, 1465, 1060 and 680; $\delta_H$(300 MHz; $C_6D_6$) 0.90 (3H, t, *J* 6.8, 15-$H_3$), 1.20–1.40 (12H, m, 9–14-$H_2$), 1.42 (2H, m, 8-$H_2$), 3.86 (2H, m, 7-$H_2$), 5.63 (1H, dd, *J* 6.4 and 14.4, 6-H), 5.79 (1H, d, *J* 7.1, 1-H), 6.10 (2H, m, 4-H and 5-H), 6.26 (1H, dd, *J* 6.8 and 10.4, 2-H) and 6.61 (1H, dd, *J* 10.5 and 14.0, 3-H); $\delta_C$(75 MHz; $C_6D_6$) 14.33 (C-15), 19.61, 23.05, 25.73, 29.98, 31.93 (C-9–14), 37.58 (C-8), 72.25 (C-7), 108.28 (C-1), 128.85 (C-3), 129.60 (C-4), 132.75 (C-2), 136.34 (C-5) and 139.88 (C-6) (Found: C, 59.64; H, 8.22. $C_{15}H_{25}BrO$ requires C, 59.80; H, 8.36%).

**(1*E*,3*E*,5*Z*)1-Bromo-7-hydroxypentadeca-1,3,5-triene 8b.** $\nu_{max}$/cm$^{-1}$ 3204, 2922, 1686, 1640, 1466, 1090 and 990; $\delta_H$(400 MHz; $C_6D_6$) 0.90 (3H, t, *J* 6.8, 15-$H_3$), 1.20–1.40 (12H, m, 9–14-$H_2$), 1.45 (2H, m, 8-$H_2$), 4.30 (2H, m, 7-$H_2$), 5.43 (1H, m, 6-H), 5.68 (1H, dd, *J* 11.5 and 15.4, 3-H), 5.91 (1H, d, *J* 13.5, 1-H), 6.32 (1H, dd, *J* 11.6 and 14.9, 4-H), 6.54 (1H, dd, *J* 11.2 and 13.5, 2-H) and 6.61 (1H, m, 5-H); $\delta_C$(100 MHz; $C_6D_6$) 14.01 (C-15), 22.75, 25.47, 29.38, 29.69, 31.90 (C-9–14), 37.66 (C-8), 67.71 (C-7), 110.00 (C-1), 128.53 (C-5), 132.45 (C-4), 136.46 (C-6), 137.40 (C-2) and 139.57 (C-3); *m*/*z* (CI, $CH_4$) 331–329 ($M^+$ + 29, 6%), 303–301 ($M^+$ + 1, 1), 285–283 (9), 221 (10), 203 (18) and 174 (100) (Found: C, 59.57; H, 8.41. $C_{15}H_{25}BrO$ requires C, 59.80; H, 8.36%).

**(10*E*,12*E*,14*Z*)-9,16-Dihydroxytetraeicosa-10,12,14-triene 9b.** $\nu_{max}$/cm$^{-1}$ 3328, 2954, 1680, 1650, 1464, 1056 and 994; $\delta_H$(300 MHz; $C_6D_6$) 0.80 (6H, m, 1-$H_3$ and 24-$H_3$), 1.00–1.20 (24H, m, 2–7-$H_2$ and 18–23-$H_2$), 1.25 (2H, m, 8-$H_2$), 1.40 (2H, m, 17-$H_2$), 4.05 (1H, m, 9-H), 4.55 (1H, m, 16-H), 5.45 (1H, t, *J* 9.8, 15-H), 5.65 (1H, dd, *J* 6.3 and 14.5, 10-H), 6.00 (1H, t, *J* 11.2, 14-H), 6.15 (1H, dd, *J* 10.8 and 14.0, 12-H), 6.25 (1H, dd, *J* 10.7 and 14.2, 11-H) and 6.55 (1H, dd, *J* 11.8 and 13.7, 13-H); $\delta_C$(75 MHz; $C_6D_6$) 14.53 (C-1 and C-24), 22.95, 23.25, 26.03, 29.42, 30.62, 32.44 (C-2–7 and C-18–23), 30.24 (C-8), 30.96 (C-17), 68.25 (C-16), 72.64 (C-9), 128.50 (C-13), 129.81 (C-14), 130.23 (C-11), 134.36 (C-12), 135.55 (C-15) and 138.55 (C-10); *m*/*z* (EI) 364 ($M^+$, 1%), 346 (M − $H_2O_3$), 328 (M − $2H_2O_3$), 141 (74), 95 (34) and 57 (100); *m*/*z* (CI, $CH_4$) 347 ($M^+$ + 1 − $H_2O$, 100%).

**Methyl (6*Z*,8*E*,10*E*,14*Z*)-5,12-dihydroxyeicosa-6,8,10,14-tetraenoate 1: $LTB_4$ methyl esters**

Under argon, a solution of Bu$^t$Li (1.80 mL of a 1.79 M solution in pentane; 2.80 mmol) was added to a solution of compound **7a** (0.22 g, 1.00 mmol) in dry $Et_2O$ (3 mL), cooled to −75 °C. The reaction mixture was stirred for 90 min and a solution of methyl 4-formylbutanoate[15] **10** (0.10 g, 1.00 mmol) in dry $Et_2O$ (2 mL) was introduced. The reaction mixture was warmed to 0 °C and stirred for 60 min before treatment with water (2 mL). After extraction with $Et_2O$ (3 × 30 mL), the organic layer was dried ($MgSO_4$) and concentrated. By silica gel column chromatography [$CH_2Cl_2$–EtOAc (80 : 20 v/v)] we isolated and identified the $LTB_4$ methyl esters **1** (0.13 g, 51%) as a yellow oil, and the acetylenic derivative **11** (0.06 g, 25%, yellow oil).

**Compound 1: $LTB_4$ methyl esters.** $\nu_{max}$/cm$^{-1}$ 3423, 2980, 1755, 1642, 1487, 1084 and 968; $\delta_H$(300 MHz; $CDCl_3$) 0.87 (3H, t, *J* 6.6, 20-$H_3$), 1.21–1.37 (6H, m, 17–19-$H_2$), 1.50–1.75 (6H, m, 3-$H_2$, 4-$H_2$, and 2 × OH), 2.02 (2H, m, 16-$H_2$), 2.33 (4H, m, 2-$H_2$ and 13-$H_2$), 3.65 (3H, s, $OCH_3$), 4.20 (1H, m, 12-H), 4.55 (1H, m, 5-H), 5.35 (2H, m, 6-H and 14-H), 5.56 (1H, m, 15-H), 5.75 (1H, dd, *J* 6.0 and 14.7, 11-H), 6.06 (1H, t, *J* 11.3, 7-H), 6.15–6.35 (2H, m, 9-H and 10-H) and 6.47 (1H, dd, *J* 11.7 and 13.5, 8-H); $\delta_C$(75 MHz; $CDCl_3$) 13.94 (C-20), 20.34 (C-3), 22.44 (C-19), 27.31 (C-16), 29.16 (C-17), 31.39 (C-18), 33.69 (C-2), 35.20 (C-13), 36.60 (C-4), 51.46 ($OCH_3$), 67.46 (C-5), 71.74 (C-12), 123.91 (C-14), 127.32 (C-8), 130.08 (C-7 and C-10), 133.51 (C-6), 133.84 (C-9), 133.94 (C-15), 136.69 (C-11) and 173.94 (C-1); *m*/*z* (EI) 333 ($M^+$ − OH, 7%), 315 (10, M − $H_2O$ − OH), 301 (9), 221 (12), 189 (14), 131 (25), 99 (68) and 61 (100) (Found: C, 71.74; H, 9.92. $C_{21}H_{34}O_4$ requires C, 71.96; H, 9.78%).

**Methyl (8E,10E,14Z)-5,12-dihydroxyeicosa-8,10,14-trien-6-ynoate 11.** $\nu_{max}$/cm$^{-1}$ 3490, 3012, 2954, 2851, 1738, 1456, 1030 and 986; $\delta_H$(300 MHz; $CDCl_3$) 0.82 (3H, t, *J* 6.5, 20-$H_3$), 1.20–1.40 (6H, m, 17–19-$H_2$), 1.70–1.80 (4H, m, 3-$H_2$ and 4-$H_2$), 2.00 (2H, m, 16-$H_2$), 2.20–2.36 (4H, m, 2-$H_2$ and 13-$H_2$), 3.62 (3H, s, $OCH_3$), 4.17 (1H, m, 12-H), 4.50 (1H, m, 5-H), 5.30 (1H, m, 15-H), 5.50–5.62 (2H, m, 8-H and 14-H), 5.78 (1H, dd, *J* 6.0 and 15.2, 11-H), 6.24 (1H, dd, *J* 10.8 and 15.2, 10-H) and 6.51 (1H, dd, *J* 10.8 and 15.5, 9-H); $\delta_C$(75 MHz; $CDCl_3$) 14.02 (C-20), 20.53 (C-3), 22.51 (C-19), 27.37 (C-16), 29.22 (C-17), 31.45 (C-18), 33.52 (C-2), 35.19 (C-13), 36.97 (C-4), 51.58 ($OCH_3$), 62.41 (C-5), 71.52 (C-12), 84.05 (C-6), 92.28 (C-7), 110.60 (C-8), 123.81 (C-14 or C-15), 129.13 (C-10), 134.06 (C-15 or C-14), 138.29 (C-11), 141.39 (C-9), and 173.93 (C-1);

*m*/*z* (CI, $CH_4$) 377 ($M^+$ + 29, 13%), 349 ($M^+$ + 1, 8), 331 (100), 313 (38), 299 (84), 219 (50) and 177 (23) (Found: C, 72.54; H, 9.12. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26%).

### Methyl (6*Z*,8*E*,10*E*)-5,12-dihydroxyeicosa-6,8,10-trienoate 2: $LTB_3$ methyl esters

In the same manner as described for the preparation of the $LTB_4$ methyl esters **1**, from (1*Z*,3*E*,5*E*)-1-bromo-7-hydroxypentadeca-1,3,5-triene **7b** we isolated and identified, after silica gel column chromatography [$CH_2Cl_2$–EtOAc (80 : 20 v/v)], the $LTB_3$ methyl esters **2** (0.14 g, 60%) as a colourless oil. $\delta_{max}$−$cm^{-1}$ 3436, 2924, 1742, 1634, 1442, 1074 and 998; $\delta_H$(400 MHz; $CDCl_3$) 0.82 (3H, t, *J* 6.3, 20-$H_3$), 1.15–1.70 (20H, m, 3-$H_2$, 4-$H_2$, 13–19-H and 2 × OH), 2.30 (2H, t, *J* 7.3, 2-$H_2$), 3.61 (3H, s, $OCH_3$), 4.10 (1H, q, *J* 6.5, 12-H), 4.53 (1H, m, 5-H), 5.36 (1H, t, *J* 10.3, 6-H), 5.70 (1H, dd, *J* 6.2 and 15.0, 11-H), 6.02 (1H, t, *J* 11.3, 7-H), 6.20 (2H, m, 9-H and 10-H) and 6.43 (1H, dd, *J* 10.9 and 15.0, 8-H); $\delta_C$(100 MHz; $CDCl_3$) 14.02 (C-20), 20.74, 22.59, 25.34, 29.20, 29.48, 29.51, 30.26, 31.81 and 37.28 (C-3, C-4 and C-13–19), 33.77 (C-2), 51.44 ($OCH_3$), 67.45 (C-12), 72.21 (C-5), 127.29 (C-10 or C-9), 129.98 (C-8 and C-10 or C-9), 133.72 (C-7), 134.02 (C-6), 137.69 (C-11) and 173.94 (C-1); *m*/*z* (EI) 334 ($M^+$ − $H_2O$, 2%), 303 (2), 219 (5), 161 (12), 129 (94) and 91 (100) (Found: C, 71.69; H, 10.08. $C_{21}H_{36}O_4$ requires C, 71.59; H, 10.23%).

### (1*E*,3*E*,5*Z*)-1-Bromo-7,7-diethoxyhepta-1,3,5-triene 4

Under argon, a solution of (2*E*,4*E*)-5-bromopenta-2,4-dienal[10a,b] **5** (0.15 g, 0.93 mmol) in dry THF (4 mL) was added to a solution of (2-ethoxyvinyl)triphenylphosphonium bromide[16] **12** (0.96 g, 2.33 mmol) in dry THF (30 mL), at room temperature. To the solution cooled to −10 °C, were added EtONa (0.30 g, 4.41 mmol) and EtOH (0.25 mL). The reaction mixture was allowed to warm to room temperature and then was heated at reflux for 12 h, filtered on Celite, and concentrated. After silica gel column chromatography [light petroleum (distilled 50–65 °C)–$Et_2O$ (70 : 30 v/v)] we isolated and identified compound **4** (0.17 g, 70%) as a yellow oil, $\nu_{max}$/$cm^{-1}$ 3062, 2974, 1608, 1562, 1322, 1118 and 992; $\delta_H$(400 MHz; $C_6D_6$) 1.10 (6H, t, *J* 7.0, 2 × $CH_3$), 3.40 (2H, m, $OCH_2CH_3$), 3.57 (2H, m, $OCH_2CH_3$), 5.30 (1H, d, *J* 5.8, 7-H), 5.62 (1H, dd, *J* 11.5 and 14.8, 3-H), 5.66 (1H, dd, *J* 5.8 and 10.8, 6-H), 5.87 (1H, d, *J* 13.6, 1-H), 5.88 (1H, t, *J* 11.2, 5-H), 6.49 (1H, dd, *J* 11.4 and 13.8, 4-H) and 6.54 (1H, dd, *J* 12.0 and 13.6, 2-H); $\delta_C$(100 MHz; $C_6D_6$) 15.54 ($CH_3$), 60.11 ($OCH_2CH_3$), 98.07 (C-7), 110.20 (C-1), 129.05 (C-4), 130.82 (C-6), 131.22 (C-2), 132.06 (C-5) and 137.64 (C-3); *m*/*z* (EI) 260–262 ($M^+$, 7%), 215–217 (21), 181 (6), 159 (5), 136 (28), 107 (29) and 79 (100) (Found: C, 50.59; H, 6.56. $C_{11}H_{17}BrO_2$ requires C, 50.72; H, 6.65%).

### (2*Z*,4*E*,6*E*,10*Z*)-1,1-Diethoxyhexadeca-2,4,6,10-tetraen-8-ol 14a

Under argon, a solution of Bu$^t$ Li (0.6 mL of a 1.7 m solution in pentane; 1.02 mmol) was added to a solution of compound **4** (0.15 g, 0.58 mmol) in dry $Et_2O$ (2 mL), cooled to −75 °C. The reaction mixture was stirred for 90 min and a solution of (3*Z*)-non-3-enal[8j] **6a** (0.20 g, 1.43 mmol) in dry $Et_2O$ (2 mL) was introduced. The reaction mixture was stirred for 2 h and then warmed to 0 °C, before treatment with water (3 mL). After extraction with $Et_2O$ (3 × 10 mL), the organic layer was dried ($MgSO_4$) and concentrated. By silica gel column chromatography [light petroleum (distilled 50–65 °C)–$Et_2O$ 50 : 50 (v/v)] we have isolated and identified the compound **14a** (0.14 g, 76%) as a yellow oil. $\nu_{max}$/$cm^{-1}$ 3428, 2956, 1628, 1456, 1330, 1126 and 999; $\delta_H$(400 MHz; $C_6D_6$) 0.85 (3H, t, *J* 7.1, 16-$H_3$), 1.10 (6H, t, *J* 7.0, 2 × $OCH_2CH_3$), 1.24 (7H, m, 13–15-$H_2$ and OH), 1.98 (2H, m, 12-$H_2$), 2.28 (2H, m, 9-$H_2$), 3.42 (2H, m, $OCH_2CH_3$), 3.60 (2H, m, $OCH_2CH_3$), 4.07 (1H, q, *J* 6.0, 8-H), 5.37 (1H, d, *J* 5.9, 1-H), 5.47 (2H, m, 10-H and 11-H), 5.59 (1H, dd, *J* 5.9 and 11.1, 2-H), 5.68 (1H, dd, *J* 6.0 and 15.1, 7-H), 6.08 (1H, dd, *J* 11.1 and 11.8, 3-H), 6.12 (1H, dd, *J* 10.9 and 14.8, 5-H), 6.28 (1H, dd, *J* 10.8 and 15.1, 6-H) and 6.73 (1H, dd, *J* 11.8 and 14.7, 4-H); $\delta_C$(100 MHz; $C_6D_6$) 13.91 (C-16), 15.21 ($OCH_2CH_3$), 22.58 (C-15), 27.41 (C-12), 29.32 (C-13), 31.47 (C-14), 35.53 (C-9), 59.85 ($OCH_2CH_3$), 71.31 (C-8), 97.93 (C-1), 124.87 (C-10), 127.86 (C-4), 128.88 (C-2), 129.73 (C-6), 131.64 (C-3), 132.62 (C-11), 134.78 (C-5) and 137.84 (C-7); *m*/*z* (EI) 322 ($M^+$, 3%), 277 (100), 259 (7), 233 (9), 211 (68), 181 (90), 155 (21), 138 (74), 110 (92), 92 (81) and 51 (70) (Found: C, 74.63; H, 10.66. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%).

### (2*Z*,4*E*,6*E*,)-1,1-Diethoxyhexadeca-2,4,6-trien-8-ol 14b

According to the procedure described for the preparation of compound **14a**, from (1*E*,3*E*,5*Z*)-1-bromo-7,7- diethoxyhepta-1,3,5-triene **4** (0.38 g, 1.46 mmol) and a solution of nonanal **6b** (4.00 g) in dry $Et_2O$ (1 mL) we isolated and identified, after silica gel column chromatography [pentane–$Et_2O$ 80 : 20 (v/v)], compound **14b** (0.37 g, 78%) as a yellow oil, $\nu_{max}$/$cm^{-1}$ 3463, 2926, 1642, 1465, 1355, 1142 and 980; $\delta_H$(400 MHz, $C_6D_6$) 0.90 (3H, t, *J* 6.9, 16-$H_3$), 1.12 (6H, t, *J* 7.1, 2 × $OCH_2CH_3$), 1.41 (14H, m, 9–15-$H_2$), 2.54 (1H, s, OH), 3.43 (2H, m, $OCH_2CH_3$), 3.57 (2H, m, $OCH_2CH_3$), 4.06 (1H, q, *J* 6.3, 8-H), 5.39 (1H, d, *J* 5.9, 1-H), 5.60 (1H, dd, *J* 5.9 and 11.1, 2-H), 5.70 (1H, dd, *J* 6.4 and 14.8, 7-H), 6.10 (1H, dd, *J* 11.0 and 11.9, 3-H), 6.13 (1H, dd, *J* 10.9 and 14.7, 5-H), 6.28 (1H, dd, *J* 10.7 and 14.9, 6-H) and 6.75 (1H, dd, *J* 11.8 and 14.5, 4-H); $\delta_C$(100 MHz, $C_6D_6$) 14.32 (C-16), 15.54 ($OCH_2CH_3$), 23.03, 25.85, 29.70, 30.00, 30.06, 32.24, 37.76 (C-9–15), 60.11 ($OCH_2CH_3$), 72.33 (C-8), 98.22 (C-1), 128.09 (C-4), 129.18 (C-2), 129.88 (C-6), 132.00 (C-3), 135.19 (C-5) and 139.03 (C-7); *m*/*z* (EI) 324 ($M^+$, 2%), 307 (10), 279 (46), 261 (10), 227 (11), 197 (6), 141 (10), 103 (100) and 85 (15) (Found: C, 74.18; H, 11.61. $C_{20}H_{36}O_3$ requires C, 74.03; H, 11.18%).

### (2*Z*,4*E*,6*E*,10*Z*)-8-Hydroxyhexadeca-2,4,6,10-tetraenal 15a

At 0 °C, aq. toluene-*p*-sulfonic acid (0.25 g in 2mL) was added to (2*Z*,4*E*,6*E*,10*Z*)-1,1-diethoxyhexadeca-2,4,6,10-tetraen-8-ol **14a** (0.19 g, 0.59 mmol) in acetone (10 mL). The mixture was stirred for 45 min, washed with saturated aq. $NaHCO_3$ (10 mL), and extracted with $Et_2O$ (3 × 10 mL). Evaporation of the dried ($MgSO_4$) solution gave crude compound **15a** (0.14 g, 95%) as a yellow oil, $\nu_{max}$/$cm^{-1}$ 3423, 2945, 2820, 1672, 1451, 1124 and 990; $\delta_H$(400 MHz; $C_6D_6$) 0.87 (3H, t, *J* 6.5, 16-$H_3$), 1.23–1.45 (7H, m, 13–15-$H_2$ and OH), 2.02 (2H, m, 12-$H_2$), 2.30 (2H, m, 9-$H_2$), 4.06 (1H, q, *J* 6.0, 8-H), 5.53 (2H, m, 10-H and 11-H), 5.69 (1H, dd, J 7.4 and 11.0, 2-H), 6.09 (1H, dd, *J* 11.0 and 14.5, 5-H), 6.07 (2H, m, 6-H and 7-H), 6.35 (1H, t, *J* 11.3, 3-H), 6.82 (1H, dd, *J* 11.3 and 14.4, 4-H) and 9.92 (1H, d, *J* 7.3, 1-H); $\delta_C$(100 MHz; $C_6D_6$) 14.05 (C-16), 17.43 (C-15), 22.27 (C-12), 24.16 (C-13), 26.32 (C-14), 30.25 (C-9), 66.05 (C-8), 122.53 (C-10), 124.56 (C-2), 127.27 (C-7 or C-6), 128.06 (C-7 or C-6), 136.10 (C-11), 136.60 (C-5), 140.37 (C-3), 145.21 (C-4) and 186.93 (C-1).

### (2*Z*,4*E*,6*E*)-8-Hydroxyhexadeca-2,4,6-trienal 15b

In the same manner as described for the preparation of **15a**, from (2*Z*,4*E*,6*E*)-1,1-diethoxyhexadeca-2,4,6-trien-8-ol **14b** (0.27 g, 0.84 mmol) we isolated and identified crude (2*Z*,4*E*,6*E*)-8-hydroxyhexadeca-2,4,6-trien **15b** (0.21 g, 100%) as a yellow oil, $\nu_{max}$/$cm^{-1}$ 3408, 2924, 2854, 1668, 1462, 1134 and 1010; $\delta_H$(200 MHz; $C_6D_6$) 0.90 (3H, t, *J* 6.2, 16-$H_3$), 1.26 (15H, m, 9–15-$H_2$ and OH), 3.92 (1H, m, 8-H), 5.61 (1H, dd, *J* 6.7 and 10.8, 2-H), 5.65 (1H, dd, *J* 11.2 and 13.8, 5-H), 6.07 (2H, m, 6-H and 7-H), 6.29 (1H, t, *J* 11.2, 3-H), 6.81 (1H, dd, *J* 11.2 and 14.2, 4-H) and 9.95 (1H, d, *J* 7.1, 1-H); $\delta_C$(50 MHz; $C_6D_6$) 14.28

(C-16), 23.06, 25.73, 29.70, 30.01, 32.24, 37.64 (C-9–15), 71.94 (C-8), 126.03 (C-2), 127.06 (C-7 or C-6), 128.76 (C-6 or C-7), 141.64 (C-5), 142.95 (C-3), 145.77 (C-4) and 189.22 (C-1).

### Methyl (6*Z*,8*E*,10*E*)-5,12-dihydroxyeicosa-6,8,10-trienoate 2: $LTB_3$ methyl esters

Under argon, a solution of Bu$^t$Li (4 mL of a 1.67 M solution in pentane; 6.68 mmol) was added to a solution of methyl 4-bromoorthobutanoate[18] (0.84 g, 3.70 mmol) in dry $Et_2O$ (10 mL), cooled to −75 °C. The reaction mixture was stirred for 90 min and a solution of compound **15b** (0.23 g, 0.93 mmol) in dry $Et_2O$ (5 mL) was introduced. The reaction mixture was warmed to 0 °C and stirred for 2 h, before treatment with aq. $CH_3COOH$ (5% w/v; 5 mL) and was then washed with water (5 mL). After extraction with $Et_2O$ (3 × 20 mL), the organic layer was dried ($MgSO_4$) and concentrated. By silica gel column chromatography [pentane–$Et_2O$ 30 : 70 (v/v)] we isolated and identified the $LTB_3$ methyl esters **2** (0.17 g, 52%) as a colourless oil. The analyses of $LTB_3$ methyl esters **2** were identical with those previously described in the case of the sample obtained from **7b** in the first manner.

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