

Total Synthesis of Leukotrienes from Butadiene

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The total synthesis of leukotrienes has been achieved starting from butadiene by a palladium-catalyzed telomerization at room temperature. A Sharpless catalytic asymmetric epoxidation generated the asymmetric centers with >94% *ee*. Simple transformations of the key intermediate **15** produced the leukotrienes LTA₄ methyl ester (**4**), LTC₄ (**1**), LTD₄ (**2**) and

LTE₄ (**3**), as well as (14*S*,15*S*)-LTA₄ methyl ester (**24**) and the novel [²H₂]-LTA₄ methyl ester (**28**). The use of the opposite chiral director in the Sharpless catalytic asymmetric epoxidation gave the key intermediate **15a** that has been used in the synthesis of the double epimers of the leukotrienes as well as LTB₄.

Introduction

The metabolism of arachidonic acid has attracted enormous attention over the years, first with the discovery of the prostaglandins via cyclooxygenase type I (COX-1)^[1] and cyclooxygenase type II (COX-2),^[2] and later on with the study of the lipoxygenase pathways leading to the biological highly potent leukotrienes^[3] and lipoxins (Figure 1).^[4] In 1938 a report by Feldberg and Kellaway described a slow reacting substance as a product of an immediate-type hypersensitivity reaction that constricted smooth muscle tissue more slowly than histamine.^[5] More than 30 years later Austen and collaborators generated larger quantities of this so called "slow-reacting substance of anaphylaxis (SRS-A)" from a mast-cell-dependent reaction, and they determined the molecular weight to be approximately 500.^[6] It required 10 more years before Samuelsson and coworkers associated SRS-A with the metabolism of arachidonic acid by the 5-lipoxygenase pathway. Corey and Samuelsson succeeded in the chemical identification of SRS-A as a mixture of leukotriene C₄, D₄ and E₄.^[7,8] The peptidoleukotrienes LTC₄ (**1**), LTD₄ (**2**) and LTE₄ (**3**) are about 1000 to 10000 times more potent than histamine on a molar basis and are involved in bronchial asthma.^[9] LTB₄, the enzymatic conversion product of the common unstable intermediate LTA₄, is a potent chemotactic agent and a modulator of inflammatory responses.^[10] More recent results have demonstrated that LTB₄ has high antiviral activity towards DNA viruses and

retroviruses, including HIV-1 and HIV-2, comparable with antiviral drugs such as Acyclovir or Ganciclovir,^[11] opening new perspectives for LTB₄ and metabolically stable LTB₄ analogs.^[12]

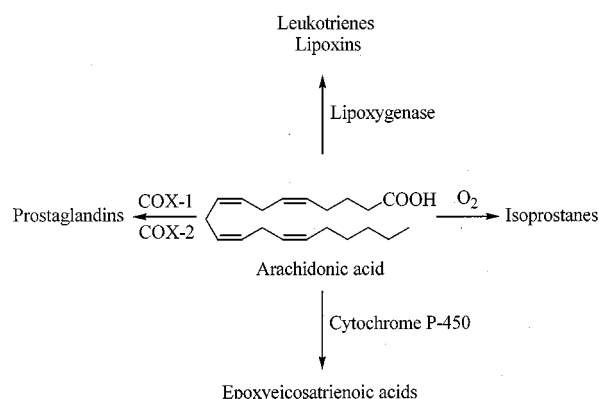


Figure 1. Metabolism of arachidonic acid

Due to the extreme scarcity from biosynthetic routes there is a need to obtain these compounds in sufficient quantities by chemical synthesis. Synthetic leukotrienes are required for biological and pharmacological research^[13] as well as for the development of specific receptor antagonists and enzyme inhibitors.^[14] Stable leukotriene analogs have been used for the isolation of enzymes involved in their formation.^[15] The leukotrienes and lipoxins derived from eicosapentaenoic acid, which are less active than their counterparts derived from arachidonic acid, have helped to understand the beneficial effects of fish oil in chronic inflammatory diseases.^[16]

As part of our ongoing interest in eicosanoids, it was our goal to develop a general asymmetric synthetic route from simple starting materials that allowed an easy access to a wide variety of lipoxygenase products.^[17]

The first stereospecific total synthesis of leukotriene A₄ methyl ester (**4**) and leukotriene C₄ (**1**) was reported by Corey using a chiral-pool strategy starting from D-ribose.^[7] In

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this route, a four-carbon chain extension using Wollenberg's reagent produced the *trans-trans* epoxydial.^[18,19] The C11–C12 *cis* double bond was introduced by a Wittig reaction to give the enantiomerically pure leukotriene A₄ methyl ester (**4**). Reaction of LTA₄ methyl ester (**4**) with reduced glutathione gave, after basic hydrolysis, leukotriene C₄ (**1**). The same chiral key intermediate was used in all later reported total syntheses.^[20] Cohan and coworkers obtained this key intermediate from D-araboascorbic acid,^[21] whereas Rokach et al.,^[22] and Bantik et al.,^[23] used different approaches from 2-deoxy-D-ribose for their chiral-pool synthesis. Baker et al. used D-glucose as the chiral starting material.^[24] The versatility of 2-deoxy-D-ribose for the synthesis of all epimers of leukotriene A₄ was shown by Rokach.^[25] D-Arabinose has been reported as the chiral source for LTA₄ and LTB₄.^[26] Isopropylidene glyceraldehyde has also served as a chiral template for several groups.^[27] Besides the chiral-pool strategies, the Sharpless enantioselective epoxidation was also successfully applied. Sharpless et al.^[28] described the conversion of methyl 7-hydroxyhept-5(*E*)-enoate and (*E*)-2,7-octadienol to the key intermediate, whereas Corey et al. used (*E*)-8-methyl-2,7-nonadien-1-ol as starting material.^[29] Tolstikov et al. described a different route from (*E*)-2,7-octadienol.^[30] A stereospecific route to (*E*)-2,7-octadienol from the propargyl alcohol, involving a selective *trans* reduction with Li in liquid NH₃, has also been reported.^[31]

Results and Discussion

In this paper we report a convergent synthesis of leukotriene A₄ methyl ester (**4**), LTC₄ (**1**), LTD₄ (**2**) and LTE₄ (**3**) as well as (14*S*,15*S*)-LTA₄ methyl ester (**24**) from butadiene by a palladium-catalyzed telomerization.

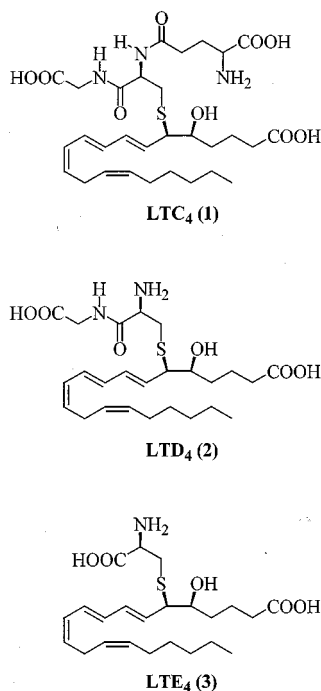
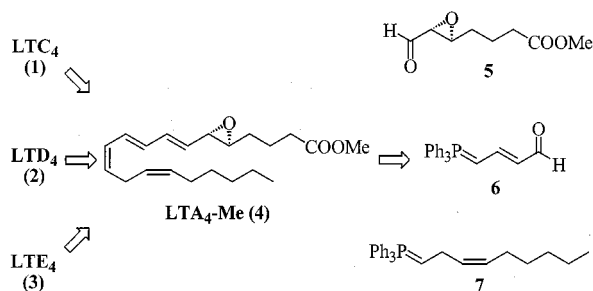


Figure 2. Slow reacting substance of anaphylaxis: leukotrienes C₄, D₄ and E₄

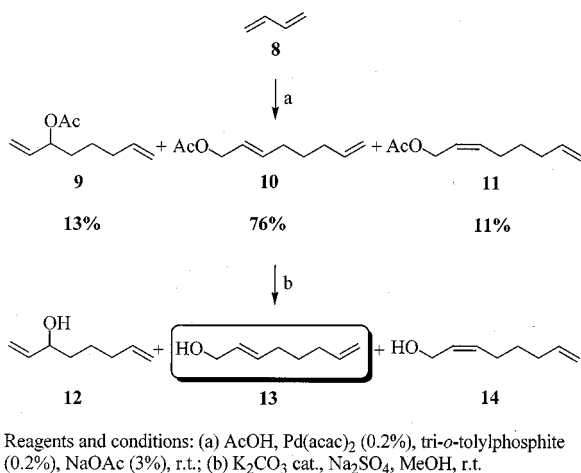
The retrosynthetic analysis of the slow reacting substance of anaphylaxis (SRS-A), LTC₄, LTD₄ and LTE₄ (Figure 2), and its precursor LTA₄ methyl ester are outlined in Scheme 1. The key intermediate **5** was obtained in an optically active form from the intermediate **18**, which was prepared from butadiene. The most convenient four-carbon homologation reagent **6** and the standard nine-carbon phosphorane **7** are the other required building blocks. LTA₄ methyl ester (**4**) can be converted into the peptidoleukotrienes **1**, **2** and **3** by S_N2 opening at C-6 with the corresponding thiols.^[7]



Scheme 1. Retrosynthetic analysis of leukotrienes C₄, D₄ and E₄

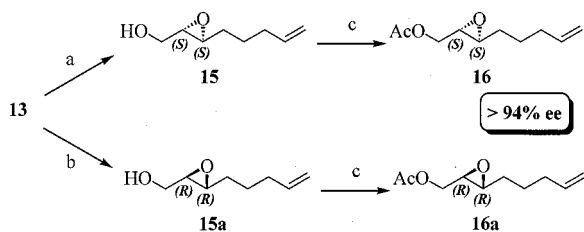
The synthesis of octadienol derivatives from butadiene is an industrial process.^[32] Most of the relevant literature refers therefore to the respective patents.^[33] A few publications describe the dimerization of butadiene at 85–90 °C in water or acetic acid in the presence of a palladium catalyst, a triphenylphosphane derivative and triethylamine.^[34] Triphenylphosphane can be replaced by tri-*o*-tolyl phosphite to give higher yields,^[35] although neither of these articles mentions the presence of 2-*cis*-octadienol acetate which accounts for more than 10% of the products formed. Longer reaction times have been reported to increase the amount of the 3-acetoxy isomer in the mixture of octadienol acetates.^[36] The temperature has little effect on the ratio of isomers. We found that the dimerization of butadiene with acetic acid in the presence of Pd(acac)₂ (0.2%), tri-*o*-tolyl phosphite (0.2%) and NaOAc (3%) can be accomplished at room temperature producing a mixture of the octadienol acetates **9** (13%), **10** (76%) and **11** (11%) (the ratio of isomers was determined by ¹H NMR spectroscopy) in 90% yield after distillation (Scheme 2).^[35] The ratio of isomers is similar to the results reported by Keim et al. using a bimetallic palladium catalyst in CH₃CN at 60 °C.^[37]

Cleavage of the acetate with a catalytic amount of K₂CO₃ in methanol at room temperature gives the octadienols **12**, **13** and **14** in 95% yield after distillation (Scheme 2). The chiral building block **15** was obtained directly from the mixture of octadienols **12**, **13** and **14** by Sharpless catalytic asymmetric epoxidation^[38] at –25 to –15 °C for six hours (60% isolated yield, 79% based on **13**) and then transformed to the acetate **16** with acetic anhydride in pyridine at 0 °C (Scheme 3). The optical purity was determined at this stage by ¹H NMR spectroscopy, using an Eu(hfc)₃ shift reagent (hfc = 3-heptafluoropropylhydroxymethylene-D-camphorate) in C₆D₆, to be >94% *ee* [ΔΔδ(OCOCH₃) = 0.06].^[39] The selectivity can be explained by the preferred epoxid-



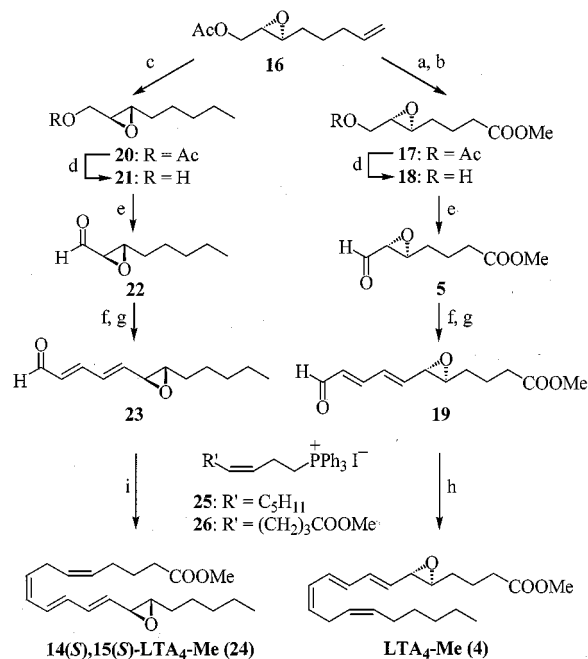
Scheme 2. Palladium-catalyzed telomerization of butadiene

ation of the *trans* allyl alcohol **13** versus the *cis* **14** and the 3-hydroxy allyl isomer **12**.^[40]

Scheme 3. Sharpless catalytic asymmetric epoxidation of **13**

The transformation of **16** to the epoxy acetate **17** was carried out as described by Sharpless (RuCl₃, NaIO₄ followed by treatment with CH₂N₂) in 71% yield after chromatography {>94% *ee* determined by ¹H NMR spectroscopy using Eu(hfc)₃ shift reagent in C₆D₆ [ΔΔδ(OC-OCH₃) = 0.04]}.^[28] The cleavage of the acetate in the presence of the epoxide and the methyl ester in **17** was readily achieved in MeOH with a catalytic amount of K₂CO₃ in the presence of anhydrous Na₂SO₄.^[41] Under these conditions neither methyl ester cleavage nor Payne rearrangement was observed. Simple filtration of the Na₂SO₄ and normal work-up gave **18** in 69% isolated yield (Scheme 4). The (*S,S*)-epoxy alcohol **18** was oxidized to the aldehyde **5** with six equivalents of Py₂·CrO₃ in CH₂Cl₂ (68% yield). The crude aldehyde **5** was reacted with the four-carbon phosphorane **6** in CH₂Cl₂ at room temperature for 15 h. Rapid filtration through SiO₂ and exposure to a catalytic amount of I₂ in CH₂Cl₂ gave the crystalline *trans-trans* epoxydienal **19** in 50% yield.^[42] Other methods using the originally described Wollenberg reagent or the double chain extension according to Rokach using two equivalents of triphenylphosphoranylidene acetaldehyde gave slightly lower yields or required preparative HPLC purification to isolate **19**. The final Wittig reaction of the phosphorane **7**, prepared in situ from the phosphonium iodide **25** with *n*BuLi at -78°C in

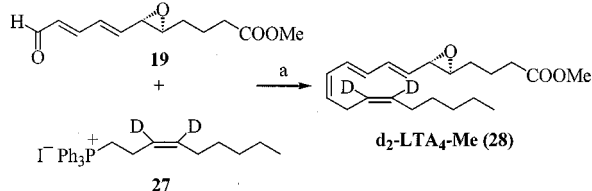
THF, with the epoxydienal **19** in the presence of 12 equivalents of HMPA gave LTA₄ methyl ester (**4**) in 63% yield after flash chromatographic purification over SiO₂ (hexane/EtOAc/Et₃N 85:5:10). The compound was characterized by ¹H NMR, ¹³C NMR, APT, COSY, and HETCOR spectroscopy, and optical rotation.^[43] Compound **4** was identical with material prepared from 2-deoxy-D-ribose.

Scheme 4. Synthesis of LTA₄ methyl ester (**4**) and (14*S*,15*S*)-LTA₄ methyl ester (**24**) from **16**

Following a similar procedure as described for the preparation of the LTA₄ methyl ester (**4**), (14*S*,15*S*)-LTA₄ methyl ester (**24**) was prepared as outlined in Scheme 4. The synthesis of (14*S*,15*S*)-LTA₄, a metabolite identified from porcine leukocyte,^[44] was obtained from the same key intermediate **16**, which was cleanly reduced to **20** [Rh (5 wt.% on alumina), 1 atm. H₂, 95% yield] {>94% *ee* determined by ¹H NMR spectroscopy using Eu(hfc)₃ shift reagent in C₆D₆ [ΔΔδ(OCOCH₃) = 0.04]}. The use of Pd/C gave lower yields due to epoxide opening.^[45] Cleavage of the acetate under the same conditions as described for **17**, with a catalytic amount of K₂CO₃ in the presence of anhydrous Na₂SO₄ in MeOH, gave the crystalline epoxy alcohol **21** in 69% yield after recrystallization from pentane; this compound was identical to a sample prepared from (*E*)-2-octen-1-ol by Sharpless epoxidation.^[46] Oxidation with Py₂·CrO₃ in CH₂Cl₂ gave the epoxy aldehyde **22** (63% isolated yield). Reaction of the aldehyde **22** with the phosphorane **6** gave a 3:1 mixture of *cis-trans* and *trans-trans* dial **23**. Isomerization of the mixture with a catalytic amount of I₂ in CH₂Cl₂ gave the crystalline *trans-trans* epoxy dial **23** in 53% yield.^[47] The final Wittig reaction of **23** with **26** in THF at

–78 °C gave (14*S*,15*S*)-LTA₄ methyl ester **24** in 63% yield after flash chromatography with EtOAc/hexane in the presence of triethylamine. The compound was characterized by ¹H NMR, ¹³C NMR, APT, COSY and HETCOR spectroscopy.

The synthesis of the novel [²H₂]-LTA₄ methyl ester (**28**) was achieved using the same strategy used for LTA₄ methyl ester (**4**) as shown in Scheme 5. In order to overcome difficulties with late-step labelling, as observed by several groups,^[48] the epoxydial **19** was coupled with the [²H₂]-labeled nine-carbon Wittig reagent (**27**) to afford the [²H₂]-LTA₄ methyl ester (**28**) in 58% yield after flash chromatography. Compound **28** was characterized by ¹H NMR, ¹³C NMR, APT, COSY and HETCOR spectroscopy.



Reagents and conditions: (a) *n*-BuLi, HMPA, THF, –78 °C.

Scheme 5. Synthesis of [²H₂]-LTA₄ methyl ester (**28**)

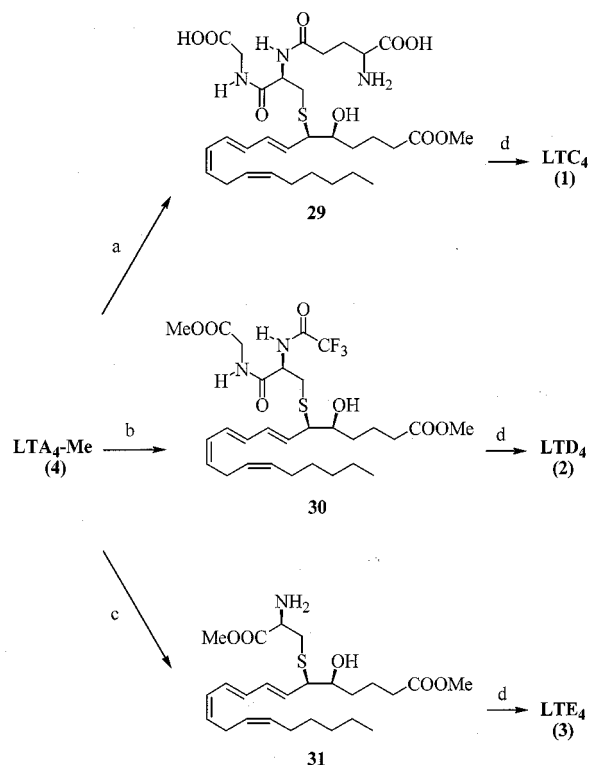
The conversion of LTA₄ methyl ester (**4**) to the peptido-leukotrienes **1**, **2** and **3** was carried out following established protocols^[21,49] as described in Scheme 6. Leukotriene C₄ (**1**), D₄ (**2**) and E₄ (**3**) could be prepared from LTA₄ methyl ester (**4**) by reaction with the free thiopeptides as described earlier^[15] or with *N*-trifluoroacetyl-L-cysteinylglycine methyl ester or L-cysteine methyl ester in the case of **2** and **3** respectively.^[8] The protected leukotrienes could be easily purified by flash chromatography and were characterized by ¹H NMR, ¹³C NMR, APT, COSY and HETCOR spectroscopy. Mild basic hydrolysis and purification using reversed phase C–18 cartridges gave the peptido-leukotrienes LTC₄ (**1**) (46% yield), LTD₄ (**2**) (63% yield) and LTE₄ (**3**) (62% yield), which were found to be identical to authentic samples (*Pharmacia&Upjohn*) by HPLC, HPLC/API–ES/MS and UV spectroscopy.

The octadienol **13** could be easily converted into the double epimer (5*R*,6*R*) **16a** using dimethyl D-tartrate as the chiral director in the Sharpless catalytic asymmetric epoxidation^[40] in similar yield and optical purity as described for **16** (Scheme 3). The conversion of **16a** to **18a** (Scheme 7) was accomplished as described for **18**.

The synthesis of the double epimeric leukotrienes from **18a** has been reported previously.^[16,22,25] The synthesis of methyl 5(*S*)-benzoyloxy-5-formylpentanoate, a key intermediate in the synthesis of leukotriene B₄,^[50] from **18a** has been achieved by regioselective Ti^{IV} isopropoxide-assisted C-3 opening of the epoxide with benzoic acid, followed by glycol cleavage (Scheme 7).^[51]

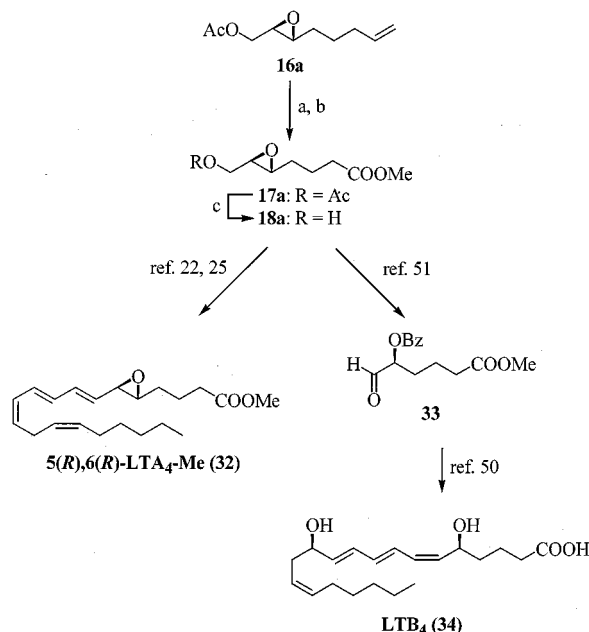
Conclusion

The palladium-catalyzed telomerization of butadiene with acetic acid at room temperature followed by Sharpless



Reagents and conditions: (a) Glutathione, Et₃N, MeOH; (b) *N*-trifluoroacetyl-L-cysteinylglycine methyl ester, Et₃N, MeOH; (c) L-cysteine methyl ester, Et₃N, MeOH; (d) 0.1 M K₂CO₃, H₂O, MeOH, 0 °C.

Scheme 6. Synthesis of LTC₄ (**1**), LTD₄ (**2**) and LTE₄ (**3**) from LTA₄ methyl ester (**4**)



Reagents and conditions: (a) NaIO₄, RuCl₃ cat., CCl₄/CH₃CN/H₂O, 0 °C; (b) CH₂N₂, Et₂O, 0 °C; (c) K₂CO₃ cat., MeOH, r.t.

Scheme 7. Synthesis of (5*R*,6*R*)-LTA₄ methyl ester (**32**) and LTB₄ (**34**) from **16a**

catalytic asymmetric epoxidation gives the chiral key-intermediates **16** and **16a** used in the synthesis of the leukotrienes, LTA₄, LTB₄, LTC₄, LTD₄, LTE₄, (14*S*,15*S*)-LTA₄,

(5R,6R)-LTA₄ and [²H₂]-LTA₄, as well as lipoxin A₄ and B₄.^[41] An easy access to the linear eicosanoids from a technical product has been achieved.

Experimental Section

General Remarks: All reactions that were moisture- and air-sensitive were carried out in flame-dried glassware and under an argon atmosphere. – The progress of the reactions was checked by thin layer chromatography (TLC) using E. Merck silica gel 60F glass plates (0.25 mm). The spots were visualized with UV light, followed by heat staining with *p*-methoxybenzaldehyde in EtOH/H₂SO₄. – Melting points were determined on a Mel–Temp capillary melting point apparatus and are uncorrected. – Silica gel 60 from EM–Science was used for flash chromatography. – HPLC analysis were performed on a Hewlett–Packard liquid chromatograph HP–1090 Series II with PV5 SDS (Solvent Delivery System) and DAD (Diode Array Detector) equipped with heated column compartment and automatic liquid injector, or on a Waters HPLC system (M–6000A pump, M–730 Data Module integrator, U6 K Injector) and a Schoeffel SF–770 UV detector. – ¹H NMR and ¹³C NMR spectroscopic data were recorded on a 300 MHz Varian Gemini 2000 Broadband high-resolution NMR spectrometer. ¹H NMR shift experiments with Eu(hfc)₃ were carried out with freshly prepared solutions of the reagent in C₆D₆ as follows: to a 5 μL sample of the corresponding acetate in 0.75 mL of C₆D₆ was added 20 μL of a solution of 150 mg (0.13 mmol) of Eu(hfc)₃ in 1 mL of C₆D₆. The %*ee* was obtained by integration of the two acetate signals. – UV Spectra were obtained using a Hewlett Packard HP–8453 UV-Visible Spectrophotometer. – Optical rotation was measured on a Perkin–Elmer Polarimeter 343. – Mass Spectra were obtained using Hewlett Packard HP–59987A API–Electrospray (Atmospheric Pressure Ionization Electrospray) interface coupled to a Mass Spectrometer Hewlett Packard HP–5989B MS.

1-Acetoxy-2,7-octadiene (10): To a mixture of palladium(II) acetylacetonate (1.2 g, 4.0 mmol), tri-*o*-tolyl phosphite (1.4 g, 4.0 mmol) and NaOAc (4.9 g, 59.7 mmol), in a pressure bottle at –10 °C, was added glacial acetic acid (48.1 mL, 0.84 mol) followed by liquid butadiene (108.2 g, 2.0 mol). The bottle was closed and the mixture was stirred at 25 °C for 10 hours. The reaction was diluted with Et₂O (400 mL) and washed successively with water (100 mL), NaHCO₃ solution (100 mL) and brine (100 mL). Drying over Na₂SO₄, concentrating under vacuo and distillation (b.p. 65 °C/1.5 mm) afforded a mixture of **9**, **10** and **11** (127.2 g, 90%) in the proportions of 13:76:11 determined by ¹H NMR spectroscopy.

10: ¹H NMR (CDCl₃, 300 MHz): δ = 1.4 (quint, *J* = 7.5 Hz, 2 H, CH₂–CH₂–CH₂), 1.9–2.0 (m and s, 7 H, CH₂–CH₂–CH₂, CH₃), 4.4 (dd, *J* = 6.4, 1.0 Hz, 2 H, CH₂O), 4.8–5.0 (m, 2 H, CH₂=), 5.5 (dt, *J* = 15.4, 6.4, 1.4 Hz, 1 H, =CH–CH₂O), 5.6–5.8 (m, 2 H, =CH–(CH₂)₃–CH=). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 20.6 (CH₃), 27.8 (CH₂–CH₂–CH₂), 31.3, 32.9 (CH₂–CH₂–CH₂), 64.9 (CH₂O), 114.5 (CH₂=), 124.0 (=CH–CH₂O), 135.8 (CH=CH–CH₂O), 138.2 (CH=CH₂), 170.6 (CO).

2,7-Octadien-1-ol (13): To a mixture of **9**, **10** and **11** (13:76:11) (51.0 g, 0.30 mol) in MeOH (300 mL) was added Na₂SO₄ (10.0 g), the suspension was aged for 10 minutes and finely powdered K₂CO₃ (5.3 g, 38.3 mmol) was added. The mixture was stirred until TLC control showed completion. The MeOH content was reduced in vacuo and the residue was diluted with Et₂O and washed with brine. Drying over Na₂SO₄, concentrating under vacuo and distilla-

tion (b.p. 60–65 °C/1.5 mm) afforded a mixture of allyl alcohols **12**, **13** and **14** (36.0 g, 95% yield).

13: ¹H NMR (CDCl₃, 300 MHz): δ = 1.4 (quint, *J* = 7.5 Hz, 2 H, CH₂–CH₂–CH₂), 1.9–2.1 (m, 4 H, CH₂–CH₂–CH₂), 2.3 (m, 1 H, OH), 4.0 (dd, *J* = 4.7, 0.4 Hz, 2 H, CH₂O), 4.8–5.0 (m, 2 H, CH₂=), 5.4–5.6 (m, 2 H, CH=CH), 5.7–5.9 (m, 1 H, CH=CH₂). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 28.2 (CH₂–CH₂–CH₂), 31.4, 33.0 (CH₂–CH₂–CH₂), 63.4 (CH₂O), 114.5 (CH₂=), 129.2 (=CH–CH₂O), 132.6 (CH=CH–CH₂O), 138.5 (CH=CH₂).

(2S,3S)-Epoxy-7-octen-1-ol (15): To a flame-dried flask under Ar was added finely pulverized 4 Å molecular sieves (15.0 g), CH₂Cl₂ (300 mL) and dimethyl L(+)-tartrate (3.9 g, 22.0 mmol). The mixture was stirred for 5 min, cooled to –20 °C and titanium(IV) isopropoxide (5.3 mL, 18.0 mmol) was rapidly added. The solution was stirred at –20 °C for 20 min and the allyl alcohol mixture (25.0 g, 0.20 mol) containing **13** was added. The stirring was continued for 15 min and the reaction was cooled to –25 °C before *tert*-butyl hydroperoxide (5–6 M anhydrous solution in decane) (90.0 mL, 0.45 mol) was added. The reaction mixture was allowed to reach –15 °C and stirred for 6 h. The reaction was quenched with a solution of iron(II) sulfate (5.0 g) and tartaric acid (2.0 g) in H₂O (50 mL). After a short exothermic reaction the mixture was stirred at room temperature for 30 min. The phases were separated and the aqueous phase re-extracted with Et₂O (2 × 250 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuo.

The crude product was then dissolved in Et₂O (300 mL) and cooled with stirring to 0 °C. 1 N NaOH (50 mL) saturated with NaCl was added at once and the mixture stirred for 30 min. The phases were separated and the organic layer washed with water (100 mL) and brine (100 mL). After drying over Na₂SO₄ the solvent was evaporated in vacuo. Purification by flash chromatography [SiO₂, hexane/EtOAc 8:2] gave **15** (17.1 g, 60%, 79% based on **13**). – [α]_D²⁰ = –34.0 (*c* = 1, CH₂Cl₂) {ref.^[30] [α]_D²⁰ = –32.7 (*c* = 0.75, CHCl₃)}. – ¹H NMR (CDCl₃, 300 MHz): δ = 1.3–1.5 [m, 4 H, (CH₂)₂–CH₂–CH=], 1.9–2.0 (m, 2 H, CH₂–CH=), 2.7–2.8 (m, 2 H, CH–O–CH), 3.3–3.5 (m, 2 H, 1 H of CH₂O, OH), 3.7 (m, 1 H, 1 H of CH₂O), 4.7–4.9 (m, 2 H, CH₂=), 5.5–5.7 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1 H, CH=CH₂). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 24.8, 30.6 [(CH₂)₂–CH₂–CH=], 32.9 (CH₂–CH=), 55.6, 58.4 (CH–O–CH), 61.6 (CH₂O), 114.6 (CH₂=), 137.9 (CH=CH₂).

(2R,3R)-Epoxy-7-octen-1-ol (15a): Following the same procedure as described for the preparation of compound **15** but using dimethyl D(–)-tartrate instead of dimethyl L(+)-tartrate, compound **13** was transformed to compound **15a**. – [α]_D²⁰ = +33.6 (*c* = 0.14, CHCl₃).

1-Acetoxy-(2S,3S)-epoxy-7-octene (16): Compound **15** (16.0 g, 0.11 mol) was dissolved in anhydrous pyridine (25 mL), cooled to 0 °C and acetic anhydride (11.3 mL, 0.12 mol) was added dropwise. The stirring was continued at room temperature until TLC control showed completion (≈12 h). The reaction mixture was diluted with Et₂O (200 mL) and added to ice water. The phases were separated and the organic layer was washed with a saturated solution of CuSO₄ (7 × 50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated under vacuo. The product was purified by distillation (b.p. 68–75 °C/1 mm) to give **16** (19.5 g, 96%). – [α]_D²⁰ = –45.0 (*c* = 1.1, CHCl₃) – ¹H NMR (CDCl₃, 300 MHz): δ = 1.4–1.7 [m, 4 H, (CH₂)₂–CH₂–CH=], 2.0–2.1 (m, 2 H, CH₂–CH=), 2.1 (s, 3 H, CH₃), 2.8–2.9 [m, 1 H, (CH₂)₃–CH–O], 2.9–3.0 (ddd, *J* = 6.3, 3.3, 2.1 Hz, 1 H, OCO–CH₂–CH–O), 3.9 (dd, *J* = 12.3, 6.3 Hz, 1 H, 1 H of CH₂O), 4.3–4.4 (dd, *J* = 12.3, 3.3 Hz, 1 H, 1

H of CH₂OCO), 4.9–5.1 (m, 2 H, CH₂=), 5.7–5.9 (ddt, J = 17.2, 10.4, 6.7 Hz, 1 H, CH=CH₂). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 20.6 (CH₃), 24.9, 30.8 [(CH₂)₂–CH₂–CH=], 33.2 (CH₂–CH=), 55.1 (O–CH–CH₂–O), 56.4 [O–CH–(CH₂)₃], 64.6 (CH₂O), 115.0 (CH₂=), 138.2 (CH=CH₂), 170.8 (CO). – [ee >94% determined by ¹H NMR spectroscopy using Eu(hfc)₃ shift reagent in C₆D₆].

1-Acetoxy-(2R,3R)-epoxy-7-octene (16a): Following the same procedure as described for the preparation of compound **16**, compound **15a** was transformed into compound **16a**. – [α]_D²⁰ = +45.1 (c = 1, CH₂Cl₂).

7-Acetoxy-(5S,6S)-epoxyheptanoic Acid Methyl Ester (17): To a stirred solution of **16** (11.2 g, 60.8 mmol) in CCl₄ (100 mL), CH₃CN (100 mL) and water (100 mL) at 0 °C was added RuCl₃·3H₂O (0.80 g, 3.1 mmol). To the black mixture was added, in portions, NaIO₄ (60.0 g, 0.28 mol). After 4 h the mixture was saturated with NaCl, diluted with Et₂O (400 mL) and filtered. The aqueous phase was extracted three times with portions of Et₂O (100 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to a volume of 20 mL. The solution was diluted with Et₂O (200 mL), cooled to 0 °C and treated with an excess of diazomethane. After 5 min the excess of diazomethane was quenched by dropwise addition of acetic acid. The organic phase was washed with a solution of NaHCO₃ (100 mL), brine (100 mL) and dried over Na₂SO₄. Concentration and flash chromatography [SiO₂, hexane/EtOAc 7:3 (5% Et₃N)] gave **17** (9.2 g, 71%). – [α]_D²⁰ = –35.8 (c = 0.42, CHCl₃). – ¹H NMR (CDCl₃, 300 MHz): δ = 1.5–1.7 [m, 2 H, CH₂–(CH₂)₂–COO], 1.7–1.9 (m, 2 H, CH₂–CH₂–COO), 2.1 (s, 3 H, CH₃–COO), 2.3–2.4 (t, J = 7.0 Hz, 2 H, CH₂–COO), 2.8–2.9 [ddd, J = 6.4, 4.7, 2.2 Hz, 1 H, (CH₂)₃–CH–O], 2.9–3.0 (ddd, J = 6.2, 3.3, 2.2 Hz, 1 H, OCO–CH₂–CH–O), 3.6 (s, 3 H, CH₃O), 3.9 (dd, J = 12.2, 6.2 Hz, 1 H, 1 H of CH₂–OCO), 4.3 (dd, J = 12.2, 3.3 Hz, 1 H, 1 H of CH₂–OCO). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 20.5 (CH₃–CO), 21.1 (CH₂–CH₂–CO), 30.6 [CH₂–(CH₂)₂–CO], 33.2 (CH₂–COO), 51.4 (CH₃O), 54.9 (O–CH–CH₂–OCO), 55.9 [O–CH–(CH₂)₃], 64.4 (CH₂OCO), 170.6 (CH₃–COO), 173.5 (COOCH₃). – [ee >94% determined by ¹H NMR spectroscopy using Eu(hfc)₃ shift reagent in C₆D₆].

7-Acetoxy-(5R,6R)-epoxyheptanoic Acid Methyl Ester (17a): Following the same procedure as described for the preparation of compound **17**, compound **16a** was transformed to compound **17a**. – [α]_D²⁰ = +35.6 (c = 0.23, CHCl₃).

(5S,6S)-Epoxy-7-hydroxyheptanoic Acid Methyl Ester (18): The acetate **17** (22.2 g, 0.10 mol) was dissolved in MeOH (200 mL) and Na₂SO₄ (15.0 g) was added. After stirring for 10 min K₂CO₃ (5.6 g, 40.5 mmol) was added. After 10 minutes the reaction was complete (TLC control). The mixture was filtered, the MeOH partially evaporated and the crude mixture diluted with CH₂Cl₂ (300 mL) and washed with brine (50 mL). After drying over Na₂SO₄ and concentrating under reduced pressure the epoxy alcohol **18** (12.1 g, 69%) was obtained. – [α]_D²⁰ = –34.0 (c = 1, CH₂Cl₂) {ref.^[22] [α]_D²⁰ = –35 (c = 2.7, CHCl₃)}. – ¹H NMR (CDCl₃, 300 MHz): δ = 1.4–1.6 [m, 2 H, CH₂–(CH₂)₂–COO], 1.6–1.8 (m, 2 H, CH₂–CH₂–COO), 2.3 (t, J = 7.3 Hz, 2 H, CH₂–COO), 2.7–2.8 (br. s, 1 H, OH), 2.8–2.9 (m, 2 H, CH–O–CH), 3.5 (dd, J = 12.6, 4.5 Hz, 1 H, 1 H of CH₂–O), 3.6 (s, 3 H, CH₃O), 3.8 (dd, J = 12.6, 2.4 Hz, 1 H, 1 H of CH₂–O). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 21.1 (CH₂–CH₂–CO), 30.6 [CH₂–(CH₂)₂–CO], 33.2 (CH₂–CO), 51.3 (CH₃O), 55.3 (CH–O), 58.2 (CH–O), 61.6 (CH₂–O), 173.7 (CO).

(5R,6R)-Epoxy-7-hydroxyheptanoic Acid Methyl Ester (18a): Following the same procedure as described for the preparation of compound **18**, compound **17a** was transformed to compound **18a**. – [α]_D²⁰ = +33.6 (c = 0.14, CHCl₃).

(5S,6R)-Epoxy-6-formylhexanoic Acid Methyl Ester (5): To a flame-dried flask under Ar were added finely powdered 4 Å molecular sieves (5.0 g) and the flask was flame dried again. Chromium(VI) oxide (33.4 g, 0.33 mol) and CH₂Cl₂ (250 mL) were added, the suspension was cooled to 10 °C and pyridine (60 mL, 0.74 mol) was added dropwise. After 1 h stirring at room temperature the reaction mixture was cooled to 15 °C and the hydroxy-epoxide **18** (10.0 g, 57.4 mmol) in CH₂Cl₂ (10 mL) was slowly added. The mixture was brought to room temperature and stirred until completion (TLC control). The crude mixture was filtered through celite, the CH₂Cl₂ was reduced to 50 mL, diluted in hexane/EtOAc (1:1) and filtered again through celite. After concentrating under vacuo the remaining pyridine was removed by azeotropic evaporation with benzene affording **5** (7.0 g, 68%). The product was used without further purification in the next step.

(5S,6S)-Epoxy-10-formyl-(7E,9E)-decadienoic Acid Methyl Ester (19): To the aldehyde **5** (7.0 g, 40.7 mmol) in CH₂Cl₂ (70 mL) was added dropwise a solution of phosphorane **6** (22.7 g, 68.7 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred for 15 h and was then diluted with hexane/EtOAc (2:1) (150 mL) and filtered through silica gel. The SiO₂ was further washed with hexane/EtOAc (1:1) and the combined fractions were dried over Na₂SO₄. The solvent was evaporated under reduced pressure affording a mixture of *cis-trans* and *trans-trans* isomers.

The crude mixture was dissolved in CH₂Cl₂ (75 mL) and crystalline iodine was added until a burgundy color remained. Stirring for 1 h produced the *trans-trans* dienal **19**. The reaction was quenched by the addition of a saturated solution of Na₂S₂O₃ (25 mL). The phases were separated, the organic layer was dried over Na₂SO₄ and concentrated under vacuo. The product was purified by flash chromatography (SiO₂, hexane/EtOAc 8:2) and the epoxy aldehyde **19** (4.5 g, 50%) was obtained as a pale-yellow solid. – ¹H NMR (CDCl₃, 300 MHz): δ = 1.5–1.7 [m, 2 H, CH₂–(CH₂)₂–COO], 1.7–1.9 (m, 2 H, CH₂–CH₂–COO), 2.3–2.4 (t, J = 6.9 Hz, 2 H, CH₂–COO), 2.9 [ddd, J = 6.3, 4.8, 2.1 Hz, 1 H, O–CH–(CH₂)₃], 3.2 (dd, J = 7.2, 2.1 Hz, 1 H, O–CH–CH=), 3.6 (s, 3 H, CH₃O), 5.9–6.0 (dd, J = 15.3, 7.2 Hz, 1 H, CH=CH–CH=CH–CO), 6.1–6.2 (dd, J = 15.3, 7.8 Hz, 1 H, =CH–CO), 6.6 (dd, J = 15.3, 11.1 Hz, 1 H, =CH–CH=CH–CO), 7.0–7.1 (ddd, J = 15.3, 11.1, 0.6 Hz, 1 H, CH=CH–CO), 9.5 (d, J = 7.8 Hz, 1 H, CHO). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 21.1 (CH₂–CH₂–CO), 31.1 [CH₂–(CH₂)₂–CO], 33.3 (CH₂–CO), 51.5 (CH₃), 57.0 (O–CH–CH=), 60.9 [O–CH–(CH₂)₃], 131.0 (=CH–CH=CH–CHO), 132.3 (=CH–CO), 141.1 (CH=CH–CH=CH–CO), 149.8 (CH=CH–CO), 173.6 (COO), 193.5 (CO).

LTA₄ Methyl Ester (4): To the phosphonium iodide **25** (3.9 g, 7.6 mmol) in THF (15 mL) at –78 °C was added dropwise *n*BuLi (1.5 M in hexane) (5.0 mL, 7.5 mmol) and the mixture stirred for 20 min to generate phosphorane **7**. Aldehyde **19** (1.5 g, 6.7 mmol) in THF (5 mL) was added followed by HMPA (14 mL, 80.5 mmol) and the mixture was stirred for 15 minutes at –78 °C. The reaction was poured into hexane/Et₂O/Et₃N 9:1:1 (250 mL; 0 °C) and washed with Na₂CO₃ solution (50 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuo affording crude **4**. Purification by flash chromatography [SiO₂, hexane/EtOAc 9:1 (10% Et₃N)] afforded LTA₄ methyl ester (**4**) (1.4 g, 63%). – [α]_D²⁰ = –23.0 (c = 0.16, cyclohexane) {ref.^[7] [α]_D²⁰ = –21.9 (cyclohexane)}. – ¹H NMR (C₆D₆, 300 MHz): δ = 0.8 (t, J = 6.9 Hz, 3 H,

$\text{CH}_3\text{--CH}_2$), 1.1–1.2 [m, 4 H, $(\text{CH}_2)_2\text{--CH}_3$], 1.2–1.4 [m, 4 H, $\text{CH}_2\text{--}(\text{CH}_2)_2\text{--COO}$, $\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 1.5–1.6 (m, 2 H, $\text{CH}_2\text{--CH}_2\text{--COO}$), 1.9–2.0 [m, 2 H, $\text{CH}_2\text{--}(\text{CH}_2)_3\text{--CH}_3$], 2.0 (t, $J = 7.5$ Hz, 2 H, $\text{CH}_2\text{--COO}$), 2.5 [dt, $J = 5.7$, 1.8 Hz, 1 H, $\text{O--CH--}(\text{CH}_2)_3$], 2.8–3.0 (m, 3 H, $=\text{CH--CH}_2\text{--CH=}$, O--CH--CH=), 3.3 (s, 3 H, CH_3O), 5.2–5.3 (dd, $J = 15.2$, 7.8 Hz, 1 H, $=\text{CH--CH--O}$), 5.3–5.5 (m, 3 H, $=\text{CH--CH}_2\text{--CH=CH}$), 6.0 (m, 1 H, $=\text{CH--CH=CH--CH}_2$), 6.1 (dd, $J = 14.9$, 10.8 Hz, 1 H, CH=CH--CH--O), 6.3 (dd, $J = 15.2$, 10.8 Hz, 1 H, CH=CH--CH--O), 6.5 (dd, $J = 14.9$, 11.7 Hz, 1 H, $=\text{CH--CH=CH--CH}_2$). – ^{13}C NMR (C_6D_6 , 75.5 MHz): $\delta = 14.1$ ($\text{CH}_3\text{--CH}_2$), 21.5 ($\text{CH}_2\text{--CH}_2\text{--CO}$), 22.8 ($\text{CH}_2\text{--CH}_3$), 26.5 ($=\text{CH--CH}_2\text{--CH=}$), 27.5 [$\text{CH}_2\text{--}(\text{CH}_2)_3\text{--CH}_3$], 29.6 (CH_2), 31.5 (CH_2), 31.7 ($\text{CH}_2\text{--CH}_2\text{--CH}_3$), 33.4 ($\text{CH}_2\text{--CO}$), 50.9 ($\text{CH}_3\text{--O}$), 57.8 (O--CH--CH=), 60.3 [$\text{O--CH--}(\text{CH}_2)_3$], 127.4 ($=\text{CH--CH}_2$), 128.8 ($=\text{CH--CH=CH--CH}_2$), 129.0 ($=\text{CH--CH=CH--CH}_2$), 131.1, 131.3, 131.4 ($=\text{CH--CH--O}$, $2 \times =\text{CH--CH}_2$), 132.2 ($\text{CH=CH--CH=CH--CH}_2$), 134.0 (CH=CH--CH--O), 172.9 (CO).

1-Acetoxy-(2S,3S)-epoxyoctane (20): Compound **16** (5.0 g, 27.1 mmol) was dissolved in EtOAc (100 mL) and Rh (5wt% on alumina) (100 mg) was added. The reaction mixture was submitted to a hydrogen atmosphere and stirred for 4 h. The hydrogen was exchanged by argon and the catalyst was filtered off. Concentration under vacuo and flash purification (SiO_2 , hexane/EtOAc 8:2) afforded **20** (4.8 g, 95%). – $[\alpha]_D^{20} = -39.0$ ($c = 1$, CH_2Cl_2). – ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.9$ (t, $J = 6.9$ Hz, 3 H, CH_3), 1.2–1.4 [m, 4 H, $(\text{CH}_2)_2\text{--CH}_3$], 1.4–1.6 [m, 4 H, $(\text{CH}_2)_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 2.1 (s, 3 H, $\text{CH}_3\text{--CO}$), 2.8–2.9 [dt, $J = 5.6$, 2.4 Hz, 1 H, $\text{O--CH--}(\text{CH}_2)_4$], 2.9–3.0 (ddd, $J = 6.3$, 3.3, 2.4 Hz, 1 H, $\text{O--CH--CH}_2\text{--OAc}$), 3.9 (dd, $J = 12.3$, 6.3 Hz, 1 H, 1 H of $\text{CH}_2\text{--OAc}$), 4.3–4.4 (dd, $J = 12.3$, 3.3 Hz, 1 H, 1 H of $\text{CH}_2\text{--OAc}$). – ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 13.8$ ($\text{CH}_3\text{--CH}_2$), 20.6 ($\text{CH}_3\text{--CO}$), 22.4 ($\text{CH}_2\text{--CH}_3$), 25.4 [$\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 31.4, 31.4 ($\text{CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_3$), 55.2 ($\text{O--CH--CH}_2\text{--OAc}$), 56.6 [$\text{O--CH--}(\text{CH}_2)_4$], 64.7 ($\text{CH}_2\text{--OAc}$), 170.8 (CO). – $[\text{ee}] > 94\%$ determined by ^1H NMR spectroscopy using $\text{Eu}(\text{hfc})_3$ shift reagent].

(2S,3S)-Epoxyoctan-1-ol (21): Acetate **20** (3.0 g, 16.1 mmol) was dissolved in MeOH (25 mL) and Na_2SO_4 (2.0 g) was added. After 10 min stirring K_2CO_3 (0.55 g, 4.0 mmol) was added and the reaction was complete after 15 minutes (TLC control). The mixture was filtered, the MeOH partially evaporated and the residue was diluted with CH_2Cl_2 (50 mL) and washed with brine (25 mL). After drying over Na_2SO_4 , concentrating under reduced pressure and recrystallizing from pentane at -20°C , epoxy alcohol **21** (1.6 g, 69%) was obtained. – M.p. $38\text{--}39^\circ\text{C}$ (ref.^[40] m.p. $38.0\text{--}39.5^\circ\text{C}$). – $[\alpha]_D^{20} = -37.0$ ($c = 1$, CH_2Cl_2) {ref.^[47] $[\alpha]_D^{20} = -44$ ($c = 1.0$, CHCl_3)}. – ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 300 MHz): $\delta = 0.8$ (t, $J = 6.9$ Hz, 3 H, CH_3), 1.1–1.3 [m, 4 H, $(\text{CH}_2)_2\text{--CH}_3$], 1.3–1.6 [m, 4 H, $(\text{CH}_2)_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 2.8–2.9 (m, 2 H, CH--O--CH), 3.1 (s, 1 H, OH), 3.5 (dd, $J = 12.6$, 4.8 Hz, 1 H, 1 H of $\text{CH}_2\text{--OH}$), 3.8 (dd, $J = 12.6$, 2.4 Hz, 1 H, 1 H of $\text{CH}_2\text{--OH}$). – ^{13}C NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 75.5 MHz): $\delta = 13.7$ (CH_3), 22.3 ($\text{CH}_2\text{--CH}_3$), 25.4 [$\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 31.4 (2 C, $\text{CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_2\text{--CH}_3$), 56.2 (CH--O), 58.7 (CH--O), 61.7 ($\text{CH}_2\text{--OH}$).

(2R,3S)-Epoxyoctanal (22): To a flame-dried flask under Ar were added finely powdered 4 Å molecular sieves (0.5 g) and the flask was flame dried again. Chromium(VI) oxide (1.2 g, 12.1 mmol) and CH_2Cl_2 (60 mL) were added and the suspension cooled to 10°C for the dropwise addition of pyridine (2.0 mL, 24.1 mmol). After 1 h stirring at room temperature the reaction mixture was cooled to 15°C and the hydroxy epoxide **21** (0.29 g, 2.01 mol) in CH_2Cl_2

(10 mL) was added. The mixture was brought to room temperature and stirred until completion (TLC control). The crude mixture was filtered through celite and concentrated under vacuo. Flash purification (SiO_2 , hexane/EtOAc 8:2) afforded **22** (0.18 g, 63%). – ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.9$ (t, $J = 7.0$ Hz, 3 H, CH_3), 1.2–1.4 [m, 4 H, $(\text{CH}_2)_2\text{--CH}_3$], 1.4–1.6 [m, 2 H, $\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 1.6–1.7 [m, 2 H, $\text{CH}_2\text{--}(\text{CH}_2)_3\text{--CH}_3$], 3.1 (dd, $J = 6.3$, 1.8 Hz, 1 H, O--CH--CHO), 3.2 (ddd, $J = 5.9$, 5.3, 1.8 Hz, 1 H, O--CH--CH_2), 9.0 (d, $J = 6.3$ Hz, 1 H, CHO). – ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 13.7$ (CH_3), 22.3 ($\text{CH}_2\text{--CH}_3$), 25.3 [$\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 31.1 (CH_2), 31.3 (CH_2), 56.7 (O--CH--CH_2), 59.1 (O--CH--CHO), 198.4 (CHO).

(6S,7S)-Epoxy-(2E,4E)-dodecadienal (23): To the aldehyde **22** (0.18 g, 1.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of phosphorane **6** (0.50 g, 1.5 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h and then concentrated to dryness. Purification by flash chromatography afforded a mixture of *cis-trans* and *trans-trans* isomers.

This mixture was dissolved in CH_2Cl_2 (10 mL) and iodine was added until a burgundy color remained. Stirring for 1 h produced the *trans-trans* dienal **23**. The reaction was quenched by addition of a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (1 mL). The phases were separated, the organic layer dried over Na_2SO_4 and concentrated under vacuo. The product was purified by flash chromatography [SiO_2 , hexane/EtOAc 9:1] and epoxy aldehyde **23** (0.13 g, 53%) was obtained as a pale-yellow solid. – $[\alpha]_D^{20} = -29.0$ ($c = 0.3$, CHCl_3) {ref.^[47] $[\alpha]_D^{20} = -27.7$ ($c = 1.0$, CHCl_3)}. – ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.9$ (t, $J = 6.9$ Hz, 3 H, CH_3), 1.2–1.8 [m, 8 H, $(\text{CH}_2)_4$], 2.9 (dt, $J = 5.6$, 1.8 Hz, 1 H, O--CH--CH_2), 3.2 (dd, $J = 7.5$, 1.8 Hz, 1 H, O--CH--CH=CH), 6.0 (dd, $J = 15.3$, 7.5 Hz, 1 H, $=\text{CH--CH--O}$), 6.2 (dd, $J = 15.3$, 7.8 Hz, 1 H, $=\text{CH--CHO}$), 6.6 (dd, $J = 15.3$, 10.8 Hz, 1 H, $=\text{CH--CH=CH--CHO}$), 7.1 (dd, $J = 15.3$, 10.8 Hz, 1 H, CH=CH--CHO), 9.6 (d, $J = 7.8$ Hz, 1 H, CHO). – ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 13.8$ (CH_3), 22.4 ($\text{CH}_2\text{--CH}_3$), 25.4 [$\text{CH}_2\text{--}(\text{CH}_2)_2\text{--CH}_3$], 31.4 (CH_2), 31.8 (CH_2), 57.3 (O--CH--CH=), 61.6 (O--CH--CH_2), 130.7 ($=\text{CH--CH=CH--CHO}$), 132.2 ($=\text{CH--CHO}$), 141.6 (O--CH--CH=), 150.1 (CH=CH--CHO), 193.7 (CHO).

(14S,15S)-LTA₄ Methyl Ester (24): To the phosphonium iodide **26** (0.60 g, 1.1 mmol) in THF (10 mL) at -78°C was added dropwise a solution of sodium bis(trimethylsilyl)amide (2.0 M in THF; 0.58 mL, 1.2 mmol). After 1 h stirring at -78°C the reaction mixture was warmed to -30°C and was kept at this temperature for 10 min. After cooling to -78°C the aldehyde **23** (0.13 g, 0.67 mmol) in THF (2 mL) was added and stirred for 30 minutes. The reaction was warmed to 0°C and quenched with Et_2O (50 mL) and Et_3N (5 mL). The mixture was washed with a saturated solution of Na_2CO_3 (10 mL) and dried over Na_2SO_4 . Concentrating under vacuo and purification by flash chromatography [SiO_2 , hexane/EtOAc 9:1 (10% Et_3N)] afforded 14(S),15(S)-LTA₄ methyl ester (**24**) (0.14 g, 63%). – ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.9$ (t, $J = 6.9$ Hz, 3 H, CH_3), 1.1–1.5 [m, 6 H, $(\text{CH}_2)_3\text{--CH}_3$], 1.5–1.6 [m, 2 H, $\text{CH}_2\text{--}(\text{CH}_2)_3\text{--CH}_3$], 1.6–1.7 (m, 2 H, $\text{CH}_2\text{--CH}_2\text{--COO}$), 2.0–2.2 [m, 2 H, $\text{CH}_2\text{--}(\text{CH}_2)_2\text{--COO}$], 2.3 (t, $J = 7.5$ Hz, 2 H, $\text{CH}_2\text{--COO}$), 2.7–3.0 [m, 3 H, $=\text{CH--CH}_2\text{--CH=}$, $\text{O--CH--}(\text{CH}_2)_4$], 3.1 (dd, $J = 8.1$, 2.1 Hz, 1 H, O--CH--CH=), 3.6 (s, 3 H, CH_3O), 5.3–5.5 (m, 4 H, $=\text{CH--CH}_2\text{--CH=CH--CH}_2$, $=\text{CH--CH--O}$), 6.0 (br. t, $J = 11.3$ Hz, 1 H, $\text{CH}_2\text{--CH=CH--CH=}$), 6.2 (dd, $J = 15.0$, 10.8 Hz, 1 H, $=\text{CH--CH=CH--CH--O}$), 6.4–6.6 (m, 2 H, CH=CH--CH--O , $\text{CH=CH--CH=CH--CH--O}$). – ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 13.8$ (CH_3), 22.4 ($\text{CH}_2\text{--CH}_3$), 24.6 ($\text{CH}_2\text{--CH}_2\text{--COO}$), 25.4

[CH₂-(CH₂)₂-CH₃], 26.0 (=CH-CH₂-CH=), 26.4 [CH₂-(CH₂)₂-COO], 31.4 (CH₂-CH₂-CH₃), 31.9 [CH₂-(CH₂)₃-CH₃], 33.2 (CH₂-COO), 51.3 (CH₃O), 58.4 (O-CH-CH=), 61.1 (O-CH-CH₂), 128.2 (CH=), 128.5 [=CH-(CH=CH-)]₂, 128.6 (CH=CH-CH=CH-CH-O), 129.4 (CH=), 130.6 (CH=), 131.2 (CH=), 131.6 (=CH-CH=CH-CH-O), 134.2 (CH=CH-CH-O), 174.0 (COO).

14,15-Dideuterio-LTA₄ Methyl Ester (28): To phosphonium iodide **27** (0.69 g, 1.3 mmol) in THF (5 mL) at -78 °C was added dropwise *n*BuLi (1.6 M in hexane; 0.84 mL, 1.3 mmol). After 20 minutes stirring, aldehyde **19** (0.15 g, 0.67 mmol) in THF (5 mL) was added followed by HMPA (1.4 mL, 8.0 mmol). The reaction mixture was stirred for 15 minutes at -78 °C, warmed to 0 °C and quenched with hexane/Et₂O/Et₃N 9:1:1. The crude reaction mixture was washed with a NaHCO₃ solution and the organic layer was dried over Na₂SO₄ and concentrated under vacuo affording crude **28**. Purification by flash chromatography [SiO₂, hexane/EtOAc 9:1 (10% Et₃N)] afforded [²H₂]-LTA₄ methyl ester (**28**) (0.13 g, 58%). - ¹H NMR (C₆D₆, 300 MHz): δ = 0.8–0.9 (t, *J* = 6.9 Hz, 3 H, CH₃-CH₂), 1.1–1.4 [m, 8 H, CH₂-(CH₂)₂-COO, (CH₂)₃-CH₃], 1.5–1.6 (m, 2 H, CH₂-CH₂-COO), 1.8–2.0 [m, 2 H, CH₂-(CH₂)₃-CH₃], 2.0 (t, *J* = 7.2 Hz, 2 H, CH₂-COO), 2.5 [dt, *J* = 5.6, 2.0 Hz, 1 H, O-CH-(CH₂)₃], 2.8–2.9 (m, 3 H, =CH-CH₂-CH=, O-CH-CH=), 3.3 (s, 3 H, CH₃O), 5.2–5.3 (dd, *J* = 15.2, 7.8 Hz, 1 H, =CH-CH-O), 5.3–5.5 (m, 1 H, =CH-CH₂-CH=), 6.0 (t, *J* = 11.1 Hz, 1 H, =CH-CH=CH-CH₂), 6.1 (dd, *J* = 14.7, 10.7 Hz, 1 H, CH=CH-CH=CH-CH₂), 6.3 (dd, *J* = 15.2, 10.7 Hz, 1 H, CH=CH-CH-O), 6.5 (dd, *J* = 14.7, 11.7 Hz, 1 H, =CH-CH=CH-CH₂). - ¹³C NMR (C₆D₆, 75.5 MHz): δ = 14.0 (CH₃-CH₂), 21.4 (CH₂-CH₂-CO), 22.7 (CH₂-CH₃), 26.3 (=CH-CH₂-CH=), 27.3 [CH₂-(CH₂)₃-CH₃], 29.5 (CH₂), 31.4 (CH₂), 31.6 (CH₂-CH₂-CH₃), 33.3 (CH₂-CO), 50.8 (CH₃O), 57.8 (O-CH-CH=), 60.2 (O-CH-CH₂), 127.0 (t, *J* = 24 Hz, CD=), 128.8 (=CH-CH=CH-CH₂), 129.0 (=CH-CH=CH-CH₂), 130.6 (t, *J* = 24 Hz, CD=), 131.3, 131.5 (=CH-CH-O, =CH-CH₂), 132.2 (CH=CH-CH=CH-CH₂), 134.0 (CH=CH-CH-O), 172.9 (CO).

LTC₄ Mono Methyl Ester (29): LTA₄ methyl ester (**4**) (40.0 mg, 0.12 mmol) was stirred under argon with glutathione (70.0 mg, 0.23 mmol) in MeOH/Et₃N (3:1, 2 mL) for 12 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography [SiO₂, step gradient from EtOAc (10% Et₃N) to MeOH] affording LTC₄ monomethyl ester (**29**) (42.5 mg, 55%). - UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. - ¹H NMR (CD₃OD, 300 MHz): δ = 0.9 (t, *J* = 6.9 Hz, 3 H, CH₃-CH₂), 1.2–1.4 [m, 8 H, CH₂-CH-OH, (CH₂)₃-CH₃], 1.5–1.9 (m, 2 H, CH₂-CH₂-COOCH₃), 2.0–2.2 [m, 4 H, CH₂-CH-NH₂, CH₂-(CH₂)₃-CH₃], 2.3 (t, *J* = 7.2 Hz, 2 H, CH₂-COOCH₃), 2.5–2.6 (m, 2 H, CH₂-CO-NH), 2.6–2.8 (dd, *J* = 13.8, 9.6 Hz, 1 H, 1 H of CH₂-S), 2.8–3.0 (m, 3 H, =CH-CH₂-CH=, 1 H of CH₂-S), 3.3–3.4 (dd, *J* = 10.1, 4.1 Hz, 1 H, CH-S), 3.6 (s, 3 H, CH₃O), 3.6–3.7 (m, 2 H, CH-OH, CH-NH₂), 3.8 (2 d AB system, *J* = 17.0 Hz, 2 H, NH-CH₂-COO), 4.5–4.6 (dd, *J* = 9.6, 4.8 Hz, 1 H, CH-NH-CO), 5.3–5.5 (m, 3 H, =CH-CH₂-CH=CH-CH₂), 5.6–5.8 (dd, *J* = 14.3, 10.1 Hz, 1 H, =CH-CH-S), 6.0 (t, *J* = 11.1 Hz, 1 H, =CH-CH=CH-CH₂), 6.1–6.3 (m, 2 H, =CH-CH=CH-CH-S), 6.6 (dd, *J* = 13.9, 11.1 Hz, 1 H, =CH-CH=CH-CH₂), 6.6 (dd, *J* = 13.9, 11.1 Hz, 1 H, =CH-CH=CH-CH₂). - ¹³C NMR (CD₃OD, 75.5 MHz): δ = 14.4 (CH₃-CH₂), 22.4 (CH₂-CH₂-COOCH₃), 23.6 (CH₂-CH₃), 27.1 (=CH-CH₂-CH=), 27.8 (CH₂-CH-NH₂), 28.1

[CH₂-(CH₂)₃-CH₃], 30.4 [CH₂-(CH₂)₂-CH₃], 32.6 (CH₂-CH₂-CH₃), 33.2 (CH₂-CH₂-CH-NH₂), 34.6 [CH₂-COOCH₃, CH₂-CH-OH (ambiguity remains)], 35.6 (CH₂-S), 43.5 (NH-CH₂-COO), 52.0 (CH₃-O), 54.5 (CH-NH-CO), 55.6 (CH-NH₂), 55.7 (CH-S), 74.1 (CH-OH), 128.5 (=CH-CH₂), 129.3 (=CH-CH=CH-CH₂), 129.8 (=CH-CH=CH-CH₂), 131.6 (=CH-CH-S), 131.7 (2 C, 2 × =CH-CH₂), 133.5 (CH=CH-CH=CH-CH₂), 134.8 (CH=CH-CH-S), 172.9, 174.1, 174.7, 175.6, 176.0 (5 CO).

LTC₄ (1): Compound **29** (42.5 mg, 0.066 mmol) was dissolved in MeOH (5 mL) and water (1 mL) under an argon atmosphere and was cooled to 0 °C for the addition of 0.1 M K₂CO₃ (2.0 mL). The reaction was followed by reversed-phase HPLC [Column: spherisorb ODS (Phenomenex) 250 × 4.6 mm, mobile phase: MeOH/0.017 M NH₄OAc (pH = 5.6) 77.5:22.5, flow rate: 0.5 mL/min, λ = 280 nm].

After 3.5 h at room temperature the reaction was quenched by neutralization with glacial acetic acid (22 μL) in water (1 mL). The solvent was evaporated under vacuo and the crude product was purified through a reversed-phase cartridge (Sep-pak) washed with MeOH (5 mL) followed by H₂O (5 mL). The product in H₂O (0.2–0.3 mL) was absorbed on the Sep-Pak cartridge. The cartridge was washed with H₂O (5 mL) and the product was eluted with H₂O/MeOH (1:1, 5 mL), H₂O/MeOH (3:7, 5 mL) and MeOH (5 mL). The amount of LTC₄ (**1**) was determined by UV analysis (ε = 49000, λ_{max} = 281 nm) to be 34.9 mg (84%). - UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. - ¹H NMR (Fraction eluted from C₁₈-cartridge with H₂O/MeOH 3:7; CD₃OD, 300 MHz): δ = 0.9 (t, *J* = 6.9 Hz, 3 H, CH₃), 1.2–1.4 [m, 6 H, (CH₂)₃-CH₃], 1.4–1.8 [m, 4 H, (CH₂)₂-CH₂-COO], 2.0–2.1 [m, 2 H, CH₂-(CH₂)₃-CH₃], 2.1–2.2 (m, 2 H, CH₂-CH-NH₂), 2.2–2.3 (t, *J* = 7.2 Hz, 2 H, CH₂-CH₂-COO), 2.5 (t, *J* = 7.1 Hz, 2 H, CH₂-CO-NH), 2.7 (dd, *J* = 14.0, 9.6 Hz, 1 H, 1 H of CH₂-S), 2.8–3.0 (m, 3 H, =CH-CH₂-CH=, 1 H of CH₂-S), 3.3–3.4 (dd, *J* = 10.2, 4.2 Hz, 1 H, CH-S), 3.6–3.7 (m, 2 H, CH-OH, CH-NH₂), 3.7 (2 d AB system, *J* = 17.1 Hz, 2 H, NH-CH₂-COO), 4.5–4.6 (dd, *J* = 9.6, 4.8 Hz, 1 H, CH-NH-CO), 5.3–5.5 (m, 3 H, =CH-CH₂-CH=CH-CH₂), 5.6–5.8 (dd, *J* = 14.1, 10.2 Hz, 1 H, =CH-CH-S), 6.0 (t, *J* = 11.1 Hz, 1 H, =CH-CH=CH-CH₂), 6.1–6.3 (m, 2 H, =CH-CH=CH-CH-S), 6.6 (dd, *J* = 13.5, 11.1 Hz, 1 H, =CH-CH=CH-CH₂). - ¹³C NMR (CD₃OD, 75.5 MHz): δ = 14.4 (CH₃), 23.0 (CH₂-CH₂-COO), 23.6 (CH₂-CH₃), 27.1 (=CH-CH₂-CH=), 27.9, 28.1 [CH₂-(CH₂)₃-CH₃, CH₂-CH-NH₂], 30.4 [CH₂-(CH₂)₂-CH₃], 32.6 (CH₂-CH₂-CH₃), 33.2 (CH₂-CH₂-CH-NH₂), 35.9 (CH₂-S), 36.5 [CH₂-CH₂-COO, CH₂-CH-OH (ambiguity remains)], 44.4 (NH-CH₂-COO), 54.4 (CH-NH-CO), 55.7 (2 C, CH-S, CH-NH₂), 74.2 (CH-OH), 128.5 (=CH-CH₂), 129.2 (=CH-CH=CH-CH₂), 129.8 (=CH-CH=CH-CH₂), 131.6, 131.7, 131.9 (2 × =CH-CH₂, =CH-CH-S), 133.6 (CH=CH-CH=CH-CH₂), 134.6 (CH=CH-CH-S), 172.6, 174.3, 175.6, 175.9, 179.9 (5 CO). - API-ES/MS (negative ionization mode): *m/z* (%) = 624 [M_{LTC4} - H⁺]⁻. - API-ES/MS (positive ionization mode): *m/z* (%) = 626 [M_{LTC4} + H⁺]⁺.

N-Trifluoroacetyl-LTD₄ Dimethyl Ester (30): Bis-*N*-trifluoroacetyl-L-cysteinylglycine dimethyl ester^[8] (1.0 g, 1.7 mmol) was added to 2,2,2-trifluoroethanol (60 mL) at room temperature. Tributylphosphane (2.2 mL, 1.8 g, 8.8 mmol) was added under Ar and the mixture was stirred for 3 h. The solvent was removed under vacuum (2 mm) and the residue was kept under high vacuum for 1 h. Washing with pentane (4 × 20 mL) and removal of the residual pentane

under vacuum afforded *N*-trifluoroacetyl-L-cysteinylglycine methyl ester (630 mg, 63%) as a white powder. The product was used directly for the reaction with LTA₄ methyl ester (**4**).

LTA₄ methyl ester (**4**) (50.0 mg, 0.15 mmol) was stirred under argon with *N*-trifluoroacetyl-L-cysteinylglycine methyl ester (86.5 mg, 0.30 mmol) in MeOH/Et₃N (3:1, 2 mL) for 4 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography (SiO₂, hexane/EtOAc/Et₃N 80:20:10) affording **30** (71.7 mg, 77%). – UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. – ¹H NMR (CDCl₃, 300 MHz): δ = 0.9 (t, *J* = 6.8 Hz, 3 H, CH₃–CH₂), 1.2–1.4 [m, 6 H, (CH₂)₃–CH₃], 1.4–1.9 [m, 4 H, (CH₂)₂–CH₂–COOCH₃], 2.3 (t, *J* = 7.1 Hz, 2 H, CH₂–COOCH₃), 2.6 (br. s, 1 H, OH), 2.7–3.1 (2 dd AB system, *J* = 14.3, 7.7 Hz, 2 H, CH₂–S), 2.9 (br. t, *J* = 7.8 Hz, 2 H, =CH–CH₂–CH=), 3.5 (dd, *J* = 9.9, 3.6 Hz, 1 H, CH–S), 3.6 (s, 3 H, CH₃O), 3.7–3.8 (m, 1 H, CH–OH), 3.8 (s, 3 H, CH₃O), 4.0–4.2 (2 dd AB system, *J* = 18.3, 5.1 Hz, *J* = 18.3, 5.4 Hz, 2 H, NH–CH₂–COO), 4.6–4.7 (m, 1 H, CH–NH), 5.3–5.5 (m, 3 H, =CH–CH₂–CH=CH–CH₂), 5.7 (dd, *J* = 14.7, 9.9 Hz, 1 H, =CH–CH–S), 6.0 (t, *J* = 11.4 Hz, 1 H, CH=CH–CH₂–CH=), 6.2 (d, *J* = 14.4, 10.8 Hz, 1 H, CH=CH–CH=CH–CH₂), 6.3 (dd, *J* = 14.7, 10.8 Hz, 1 H, CH=CH–CH–S), 6.5–6.6 (dd, *J* = 14.4, 11.4 Hz, 1 H, =CH–CH=CH–CH₂), 7.0 (t, *J* = 5.4 Hz, 1 H, NH–CH₂), 7.6 (br. d, *J* = 6.9 Hz, 1 H, NHCOCF₃). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 13.9, 20.9, 22.5, 26.2, 27.2, 29.2, 31.4, 32.8, 33.5, 33.6, 41.4, 51.5, 52.5, 53.0, 55.6, 72.9, 127.0, 128.3, 128.6, 129.3, 131.1, 131.4, 132.1, 135.0, 168.9, 169.8, 174.3. The signals of the carbons COCF₃ were not observed due to the low intensity.

LTD₄ (2): Compound **30** (71.7 mg, 0.12 mmol) was dissolved under an argon atmosphere in MeOH (5 mL) and water (1 mL), cooled to 0 °C and 0.1 M K₂CO₃ (6.0 mL) was added. After 3.5 h the reaction was quenched by neutralization with glacial acetic acid (66 μ L) in water (1 mL). Concentration under vacuo and purification through a reversed-phase cartridge (Sep–pak), as described for compound **1**, afforded LTD₄ (**2**) (49.0 mg, 82%). – UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. – API-ES/MS (negative ionization mode): *m/z* (%) = 495 [M_{LTD4} – H⁺][–]. – API-ES/MS (positive ionization mode): *m/z* (%) = [M_{LTD4} + H⁺]⁺, 319 [M_{LTD4} – (Gly–cys) + H⁺]⁺.

LTE₄ Dimethyl Ester (31): LTA₄ methyl ester (**4**) (67.0 mg, 0.20 mmol) was stirred with L-cysteine methyl ester hydrochloride (69.0 mg, 0.40 mmol) in MeOH/Et₃N (3:1, 2 mL) under argon for 5 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography (SiO₂, hexane/EtOAc/Et₃N 50:50:10) affording **31** (70.1 mg, 75%). – UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. – ¹H NMR (C₆D₆, 300 MHz): δ = 1.0 (t, 3 H, *J* = 6.8 Hz, CH₃), 1.3–1.5 [m, 6 H, (CH₂)₃–CH₃], 1.5–1.7 (m, 2 H, CH₂–CH–OH), 1.7–2.1 (m, 2 H, CH₂–CH₂–COO), 2.1 (m, 2 H, =CH–CH₂–CH₂), 2.2 (t, *J* = 14.4 Hz, 2 H, CH₂–COOCH₃), 2.8 (dd AB system, *J* = 13.8, 6.6 Hz, 1 H, 1 H of CH₂–S), 2.9 (2 dd AB system, *J* = 13.8, 5.1 Hz, 1 H, 1 H of CH₂–S), 3.0 (br. t, *J* = 6.3 Hz, 2 H, =CH–CH₂–CH=), 3.4–3.5 (2 s, 6 H, 2 $\times$ CH₃O), 3.5–3.6 (m, 2 H, CH–S, CH–NH₂), 3.8 (dt, *J* = 9.0, 3.8 Hz, 1 H, CH–OH), 5.4–5.5 (m, 3 H, =CH–CH₂–CH=CH–CH₂), 5.9 (dd, *J* = 14.4, 9.6 Hz, 1 H, =CH–CH–S), 6.1 (t, *J* = 11.1 Hz, 1 H, =CH–CH=CH–CH₂), 6.1–6.3 (m, 2 H, =CH–CH=CH–CH–S), 6.6 (dd, *J* = 14.1, 11.1 Hz, 1 H, =CH–CH=CH–CH₂). – ¹³C NMR (C₆D₆, 75.5 MHz): δ = 14.0 (CH₃–CH₂), 21.7 (CH₂–CH₂–COO), 22.7 (CH₂–CH₃), 26.4 (=CH–CH₂–CH=), 27.4 [CH₂–(CH₂)₃–CH₃], 29.5 [CH₂–(CH₂)₂–CH₃], 31.6

(CH₂–CH₂–CH₃), 33.7 (CH₂–COO), 34.3 (CH₂–CH–OH), 35.4 (CH₂–S), 50.8 (CH₃O), 51.5 (CH₃O), 54.7, 55.6 (CH–NH₂, CH–S), 72.9 (CH–OH), 127.6 (=CH–CH₂), 128.1 (CH=CH–CH=CH–CH–S), 129.1 (=CH–CH=CH–CH₂), 130.7 (=CH–CH–S), 131.0 (=CH–CH₂), 131.0 (=CH–CH₂), 132.7 (=CH–CH=CH–CH–S), 134.0 (CH=CH–CH–S), 173.5 (COO), 174.2 (COO).

LTE₄ (3): Compound **31** (70.1 mg, 0.15 mmol) was dissolved in MeOH (5 mL) and water (1 mL) under an argon atmosphere, cooled to 0 °C and 0.1 M K₂CO₃ (4.0 mL) was added. After 3.5 h the reaction was quenched by neutralization with glacial acetic acid (44 μ L) in water (1 mL). Concentration under vacuo and purification through a reversed-phase cartridge, as described for compound **1**, afforded LTE₄ (**3**) (54.4 mg, 82%). – UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. – API ES/MS (negative ionization mode): *m/z* (%) = 438 [M_{LTE4} – H⁺][–].

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