Total Synthesis of Leukotrienes from Butadiene

Ana Rodríguez,[a] Miguel Nomen,[a][†] Bernd W. Spur,*[a,c] Jean-Jacques Godfroid,[b] and Tak H. Lee[c]

Keywords: Palladium / Telomerization / Eicosanoids / Asymmetric synthesis / Epoxidations

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 LTA_4 methyl ester (**4**), LTC_4 (**1**), LTD_4 (**2**) and LTE_4 (**3**), as well as (14*S*,15*S*)-LTA_4 methyl ester (**24**) and the novel [$^2H_2$]-LTA_4 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 LTB_4.

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 C_4, D_4 and E_4.[7,8] The peptidoleukotrienes LTC_4 (**1**), LTD_4 (**2**) and LTE_4 (**3**) are about 1000 to 10000 times more potent than histamine on a molar basis and are involved in bronchial asthma.[9] LTB_4, the enzymatic conversion product of the common unstable intermediate LTA_4, is a potent chemotactic agent and a modulator of inflammatory responses.[10] More recent results have demonstrated that LTB_4 has high antiviral activity towards DNA viruses and retroviruses, including HIV-1 and HIV-2, comparable with antiviral drugs such as Acylovir or Ganciclovir,[11] opening new perspectives for LTB_4 and metabolically stable LTB_4 analogs.[12]

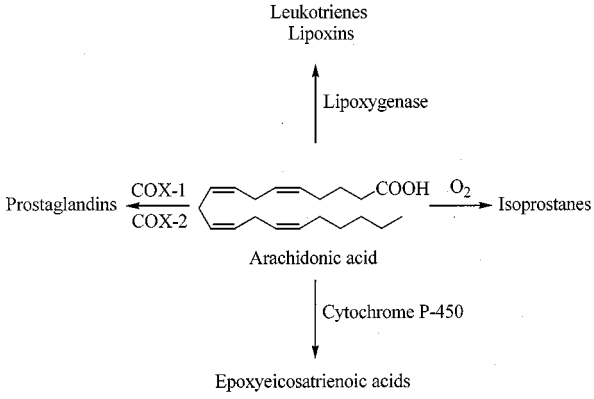


Figure 1. Metabolism of arachidonic acid

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 A_4 methyl ester (**4**) and leukotriene C_4 (**1**) was reported by Corey using a chiral-pool strategy starting from D-ribose.[7] In

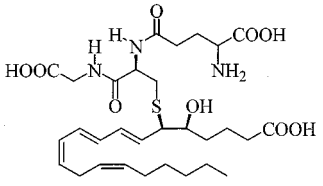
[a] Department of Cell Biology, University of Medicine and Dentistry of New Jersey, SOM,
2, Medical Center Drive, Stratford, NJ 08084, USA
Fax: (internat.) +1-856/566-6195
E-mail: spubw@umdnj.edu
[b] Laboratoire de Pharmacochimie Moleculaire,
Universite Paris 7,
Paris 75251, France
[c] Department of Respiratory Medicine and Allergy, King's College London, Guy's Hospital,
London SE1 9RT, UK
[†] Deceased September 26, 1997

  1434−193X/00/0917−2991 $ 17.50+.50/0

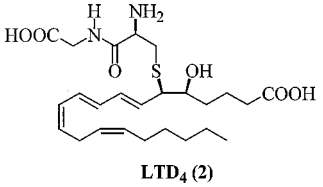
this route, a four-carbon chain extension using Wollenberg's reagent produced the *trans-trans* epoxydienal.[18,19] The C11−C12 *cis* double bond was introduced by a Wittig reaction to give the enantiomerically pure leukotriene A_4 methyl ester (**4**). Reaction of LTA_4 methyl ester (**4**) with reduced glutathione gave, after basic hydrolysis, leukotriene C_4 (**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 A_4 was shown by Rokach.[25] D-Arabinose has been reported as the chiral source for LTA_4 and LTB_4.[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 NH_3, has also been reported.[31]

Results and Discussion

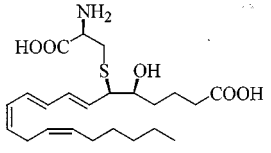
In this paper we report a convergent synthesis of leukotriene A_4 methyl ester (**4**), LTC_4 (**1**), LTD_4 (**2**) and LTE_4 (**3**) as well as (14*S*,15*S*)-LTA_4 methyl ester (**24**) from butadiene by a palladium-catalyzed telomerization.



LTC_4 (1)



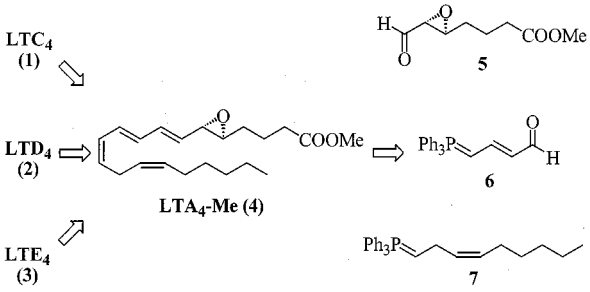
LTD_4 (2)



LTE_4 (3)

Figure 2. Slow reacting substance of anaphylaxis: leukotrienes C_4, D_4 and E_4

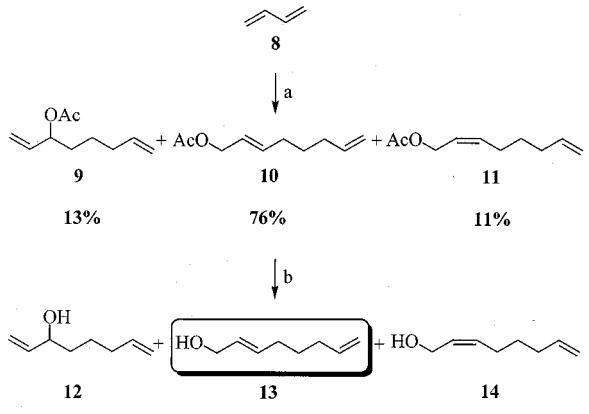
The retrosynthetic analysis of the slow reacting substance of anaphylaxis (SRS-A), LTC_4, LTD_4 and LTE_4 (Figure 2), and its precursor LTA_4 methyl ester are outlined in Scheme 1. The key intermediate **5** was obtained in an optically active form from the intermediate **18**, which was prepared from butadiene. The most convenient four-carbon homologation reagent **6** and the standard nine-carbon phosphorane **7** are the other required building blocks. LTA_4 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 C_4, D_4 and E_4

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 CH_3CN at 60 °C.[37]

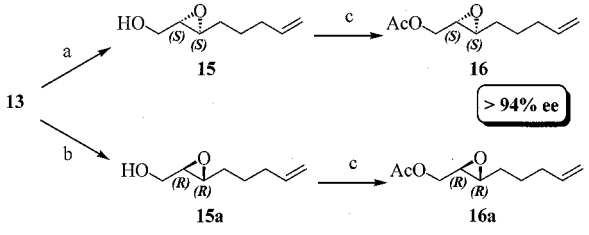
Cleavage of the acetate with a catalytic amount of K_2CO_3 in methanol at room temperature gives the octadienols **12**, **13** and **14** in 95% yield after distillation (Scheme 2). The chiral building block **15** was obtained directly from the mixture of octadienols **12**, **13** and **14** by Sharpless 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 C_6D_6, to be >94% *ee* [$\Delta\Delta\delta(OCOCH_3) = 0.06$].[39] The selectivity can be explained by the preferred epoxid-



Reagents and conditions: (a) AcOH, $Pd(acac)_2$ (0.2%), tri-*o*-tolylphosphite (0.2%), NaOAc (3%), r.t.; (b) K_2CO_3 cat., Na_2SO_4, MeOH, r.t.

Scheme 2. Palladium-catalyzed telomerization of butadiene

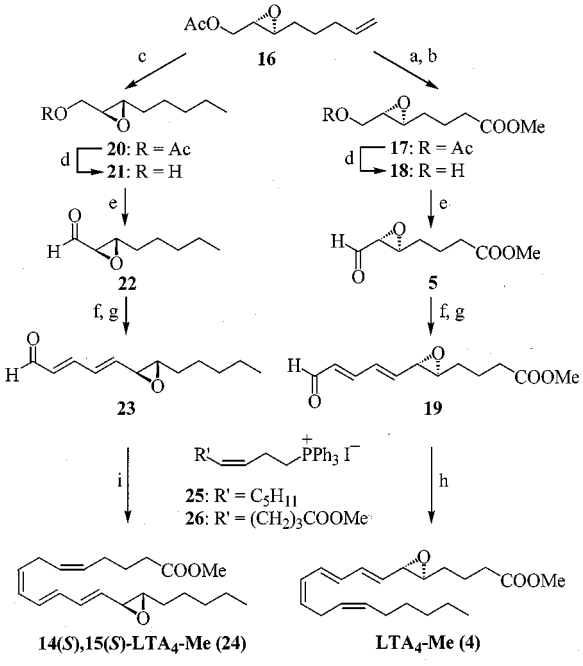
ation of the *trans* allyl alcohol **13** versus the *cis* **14** and the 3-hydroxy allyl isomer **12**.[40]



Reagents and conditions: (a) Dimethyl L(+)-tartrate (11%), Ti(i-PrO)$_4$ (9%), TBHP (2.2 equiv.), 4 Å molecular sieves, CH_2Cl_2, -25°C→ -15°C; (b) Dimethyl D(-)-tartrate (11%), Ti(i-PrO)$_4$ (9%), TBHP (2.2 equiv.), 4 Å molecular sieves, CH_2Cl_2, -25°C→ -15°C; (c) Ac_2O, pyridine, 0°C, 12 h.

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

The transformation of **16** to the epoxy acetate **17** was carried out as described by Sharpless ($RuCl_3$, $NaIO_4$ followed by treatment with CH_2N_2) in 71% yield after chromatography {>94% *ee* determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent in C_6D_6 [$\Delta\Delta\delta$(OCOCH$_3$) = 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 K_2CO_3 in the presence of anhydrous Na_2SO_4.[41] Under these conditions neither methyl ester cleavage nor Payne rearrangement was observed. Simple filtration of the Na_2SO_4 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 $Py_2{\cdot}CrO_3$ in CH_2Cl_2 (68% yield). The crude aldehyde **5** was reacted with the four-carbon phosphorane **6** in CH_2Cl_2 at room temperature for 15 h. Rapid filtration through SiO_2 and exposure to a catalytic amount of I_2 in CH_2Cl_2 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 LTA_4 methyl ester (**4**) in 63% yield after flash chromatographic purification over SiO_2 (hexane/EtOAc/Et_3N 85:5:10). The compound was characterized by ^{1}H NMR, ^{13}C NMR, APT, COSY, and HETCOR spectroscopy, and optical rotation.[43] Compound **4** was identical with material prepared from 2-deoxy-D-ribose.



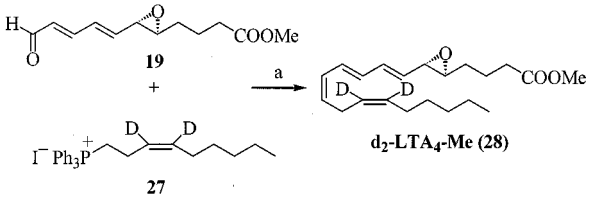
Reagents and conditions: (a) $NaIO_4$, $RuCl_3$ cat., $CCl_4/CH_3CN/H_2O$, 0°C; (b) CH_2N_2, Et_2O, 0°C; (c) H_2, Rh (5 wt.% on alumina), EtOAc, r.t.; (d) K_2CO_3 cat., MeOH, r.t.; (e) $Py_2{\cdot}CrO_3$, CH_2Cl_2; (f) (*trans*)Ph_3P=CH-CH=CH-CHO (**6**), CH_2Cl_2; (g) I_2, CH_2Cl_2; (h) **25**, *n*-BuLi, HMPA, THF, -78°C; (i) **26**, $NaN(TMS)_2$, THF, -78°C.

Scheme 4. Synthesis of LTA_4 methyl ester (**4**) and (14*S*,15*S*)-LTA_4 methyl ester (**24**) from **16**

Following a similar procedure as described for the preparation of the LTA_4 methyl ester (**4**), (14*S*,15*S*)-LTA_4 methyl ester (**24**) was prepared as outlined in Scheme 4. The synthesis of (14*S*,15*S*)-LTA_4, 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. H_2, 95% yield] {>94% *ee* determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent in C_6D_6 [$\Delta\Delta\delta$(OCOCH$_3$) = 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 K_2CO_3 in the presence of anhydrous Na_2SO_4 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 $Py_2{\cdot}CrO_3$ in CH_2Cl_2 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* dienal **23**. Isomerization of the mixture with a catalytic amount of I_2 in CH_2Cl_2 gave the crystalline *trans-trans* epoxy dienal **23** in 53% yield.[47] The final Wittig reaction of **23** with **26** in THF at

−78 °C gave (14*S*,15*S*)-LTA_4 methyl ester **24** in 63% yield after flash chromatography with EtOAc/hexane in the presence of triethylamine. The compound was characterized by ^1H NMR, ^{13}C NMR, APT, COSY and HETCOR spectroscopy.

The synthesis of the novel [$^2H_2$]-LTA_4 methyl ester (**28**) was achieved using the same strategy used for LTA_4 methyl ester (**4**) as shown in Scheme 5. In order to overcome difficulties with late-step labelling, as observed by several groups,[48] the epoxydienal **19** was coupled with the [$^2H_2$]-labeled nine-carbon Wittig reagent (**27**) to afford the [$^2H_2$]-LTA_4 methyl ester (**28**) in 58% yield after flash chromatography. Compound **28** was characterized by ^1H NMR, ^{13}C NMR, APT, COSY and HETCOR spectroscopy.



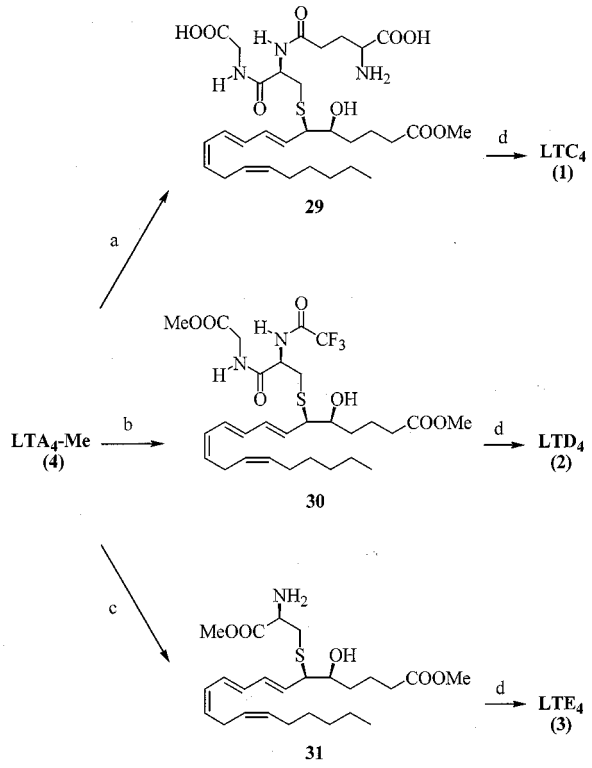
Reagents and conditions: (a) *n*-BuLi, HMPA, THF, -78°C.

Scheme 5. Synthesis of [$^2H_2$]-LTA_4 methyl ester (**28**)

The conversion of LTA_4 methyl ester (**4**) to the peptidoleukotrienes **1**, **2** and **3** was carried out following established protocols[21,49] as described in Scheme 6. Leukotriene C_4 (**1**), D_4 (**2**) and E_4 (**3**) could be prepared from LTA_4 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, ^{13}C NMR, APT, COSY and HETCOR spectroscopy. Mild basic hydrolysis and purification using reversed phase C−18 cartridges gave the peptidoleukotrienes LTC_4 (**1**) (46% yield), LTD_4 (**2**) (63% yield) and LTE_4 (**3**) (62% yield), which were found to be identical to authentic samples (*Pharmacia&Upjohn*) by HPLC, HPLC/API−ES/MS and UV spectroscopy.

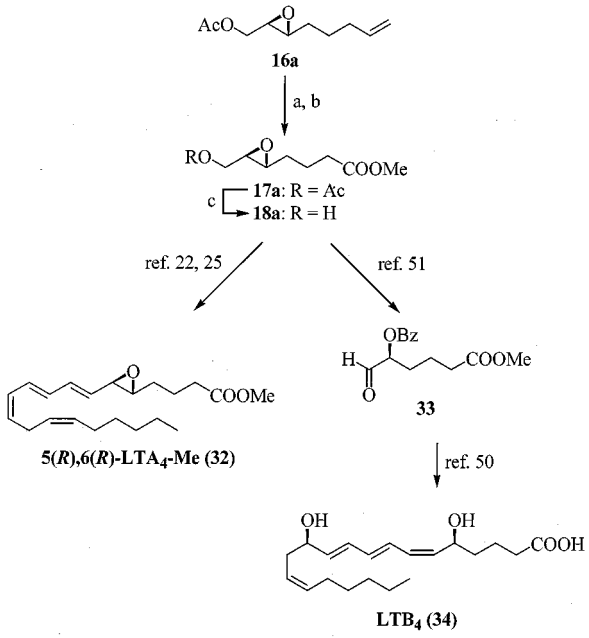
The octadienol **13** could be easily converted into the double epimer (5*R*,6*R*) **16a** using dimethyl D-tartrate as the chiral director in the Sharpless catalytic asymmetric epoxidation[40] in similar yield and optical purity as described for **16** (Scheme 3). The conversion of **16a** to **18a** (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 B_4,[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]



Reagents and conditions: (a) Glutathione, Et_3N, MeOH; (b) *N*-trifluoroacetyl-L-cysteinylglycine methyl ester, Et_3N, MeOH; (c) L-cysteine methyl ester, Et_3N, MeOH; (d) 0.1 M K_2CO_3, H_2O, MeOH, 0°C.

Scheme 6. Synthesis of LTC_4 (**1**), LTD_4 (**2**) and LTE_4 (**3**) from LTA_4 methyl ester (**4**)



Reagents and conditions: (a) $NaIO_4$, $RuCl_3$ cat., $CCl_4/CH_3CN/H_2O$, 0°C; (b) CH_2N_2, Et_2O, 0°C; (c) K_2CO_3 cat., MeOH, r.t.

Scheme 7. Synthesis of (5*R*,6*R*)-LTA_4 methyl ester (**32**) and LTB_4 (**34**) from **16a**

Conclusion

The palladium-catalyzed telomerization of butadiene with acetic acid at room temperature followed by Sharpless catalytic asymmetric epoxidation gives the chiral key-intermediates **16** and **16a** used in the synthesis of the leukotrienes, LTA_4, LTB_4, LTC_4, LTD_4, LTE_4, (14*S*,15*S*)-LTA_4,

(5*R*,6*R*)-LTA_4 and [$^2H_2$]-LTA_4, as well as lipoxin A_4 and B_4.[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/H_2SO_4. − 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 ^{13}C 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 C_6D_6 as follows: to a 5μL sample of the corresponding acetate in 0.75 mL of C_6D_6 was added 20 μL of a solution of 150 mg (0.13 mmol) of Eu(hfc)$_3$ in 1 mL of C_6D_6. 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 Et_2O (400 mL) and washed successively with water (100 mL), $NaHCO_3$ solution (100 mL) and brine (100 mL). Drying over Na_2SO_4, 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 ($CDCl_3$, 300 MHz): δ = 1.4 (quint, *J* = 7.5 Hz, 2 H, $CH_2-CH_2-CH_2$), 1.9−2.0 (m and s, 7 H, $CH_2-CH_2-CH_2$, CH_3), 4.4 (dd, *J* = 6.4, 1.0 Hz, 2 H, CH_2O), 4.8−5.0 (m, 2 H, $CH_2=$), 5.5 (dtt, *J* = 15.4, 6.4, 1.4 Hz, 1 H, $=CH-CH_2O$), 5.6−5.8 (m, 2 H, $=CH-(CH_2)_3-CH=$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.6 (CH_3), 27.8 ($CH_2-CH_2-CH_2$), 31.3, 32.9 ($CH_2-CH_2-CH_2$), 64.9 (CH_2O), 114.5 ($CH_2=$), 124.0 ($=CH-CH_2O$), 135.8 ($CH=CH-CH_2O$), 138.2 ($CH=CH_2$), 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 Na_2SO_4 (10.0 g), the suspension was aged for 10 minutes and finely powdered K_2CO_3 (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 Et_2O and washed with brine. Drying over Na_2SO_4, concentrating under vacuo and distillation (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 ($CDCl_3$, 300 MHz): δ = 1.4 (quint, *J* = 7.5 Hz, 2 H, $CH_2-CH_2-CH_2$), 1.9−2.1 (m, 4 H, $CH_2-CH_2-CH_2$), 2.3 (m, 1 H, OH), 4.0 (dd, *J* = 4.7, 0.4 Hz, 2 H, CH_2O), 4.8−5.0 (m, 2 H, $CH_2=$), 5.4−5.6 (m, 2 H, $CH=CH$), 5.7−5.9 (m, 1 H, $CH=CH_2$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 28.2 ($CH_2-CH_2-CH_2$), 31.4, 33.0 ($CH_2-CH_2-CH_2$), 63.4 (CH_2O), 114.5 ($CH_2=$), 129.2 ($=CH-CH_2O$), 132.6 ($CH=CH-CH_2O$), 138.5 ($CH=CH_2$).

(2*S*,3*S*)-Epoxy-7-octen-1-ol (15): To a flame-dried flask under Ar was added finely pulverized 4 A molecular sieves (15.0 g), CH_2Cl_2 (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 H_2O (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 Et_2O (2 × 250 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuo.
The crude product was then dissolved in Et_2O (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 Na_2SO_4 the solvent was evaporated in vacuo. Purification by flash chromatography [SiO_2, hexane/EtOAc 8:2] gave **15** (17.1 g, 60%, 79% based on **13**). − $[\alpha]_D^{20}$ = −34.0 (*c* = 1, CH_2Cl_2) {ref.[30] $[\alpha]_D^{20}$ = −32.7 (*c* = 0.75, $CHCl_3$)}. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.3−1.5 [m, 4 H, $(CH_2)_2-CH_2-CH=$], 1.9−2.0 (m, 2 H, $CH_2-CH=$), 2.7−2.8 (m, 2 H, $CH-O-CH$), 3.3−3.5 (m, 2 H, 1 H of CH_2O, OH), 3.7 (m, 1 H, 1 H of CH_2O), 4.7−4.9 (m, 2 H, $CH_2=$), 5.5−5.7 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1 H, $CH=CH_2$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.8, 30.6 [$(CH_2)_2-CH_2-CH=$], 32.9 ($CH_2-CH=$), 55.6, 58.4 ($CH-O-CH$), 61.6 (CH_2O), 114.6 ($CH_2=$), 137.9 ($CH=CH_2$).

(2*R*,3*R*)-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**. − $[\alpha]_D^{20}$ = +33.6 (*c* = 0.14, $CHCl_3$) .

1-Acetoxy-(2*S*,3*S*)-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 Et_2O (200 mL) and added to ice water. The phases were separated and the organic layer was washed with a saturated solution of $CuSO_4$ (7 × 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuo. The product was purified by distillation (b.p. 68−75 °C/1 mm) to give **16** (19.5 g, 96%). − $[\alpha]_D^{20}$ = −45.0 (*c* = 1.1, $CHCl_3$) − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.4−1.7 [m, 4 H, $(CH_2)_2-CH_2-CH=$], 2.0−2.1 (m, 2 H, $CH_2-CH=$), 2.1 (s, 3 H, CH_3), 2.8−2.9 [m, 1 H, $(CH_2)_3-CH-O$], 2.9−3.0 (ddd, *J* = 6.3, 3.3, 2.1 Hz, 1 H, $OCO-CH_2-CH-O$), 3.9 (dd, *J* = 12.3, 6.3 Hz, 1 H, 1 H of CH_2O), 4.3−4.4 (dd, *J* = 12.3, 3.3 Hz, 1 H, 1

H of CH_2OCO), 4.9−5.1 (m, 2 H, CH_2=), 5.7−5.9 (ddt, J = 17.2, 10.4, 6.7 Hz, 1 H, C*H*=CH_2). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.6 (CH_3), 24.9, 30.8 [(CH_2)$_2$−CH_2−CH=], 33.2 (CH_2−CH=), 55.1 (O−*C*H−CH_2−O), 56.4 [O−*C*H−(CH_2)$_3$], 64.6 (CH_2O), 115.0 (CH_2=), 138.2 (*C*H=CH_2), 170.8 (CO). − [*ee* >94% determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent in C_6D_6].

1-Acetoxy-(2*R*,3*R*)-epoxy-7-octene (16a): Following the same procedure as described for the preparation of compound **16**, compound **15a** was transformed into compound **16a**. − $[\alpha]_D^{20}$ = +45.1 (c = 1, CH_2Cl_2).

7-Acetoxy-(5*S*,6*S*)-epoxyheptanoic Acid Methyl Ester (17): To a stirred solution of **16** (11.2 g, 60.8 mmol) in CCl_4 (100 mL), CH_3CN (100 mL) and water (100 mL) at 0 °C was added $RuCl_3$·3H_2O (0.80 g, 3.1 mmol). To the black mixture was added, in portions, $NaIO_4$ (60.0 g, 0.28 mol). After 4 h the mixture was saturated with NaCl, diluted with Et_2O (400 mL) and filtered. The aqueous phase was extracted three times with portions of Et_2O (100 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a volume of 20 mL. The solution was diluted with Et_2O (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 $NaHCO_3$ (100 mL), brine (100 mL) and dried over Na_2SO_4. Concentration and flash chromatography [SiO_2, hexane/EtOAc 7:3 (5% Et_3N)] gave **17** (9.2 g, 71%). − $[\alpha]_D^{20}$ = −35.8 (c = 0.42, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.5−1.7 [m, 2 H, C*H*$_2$−(CH_2)$_2$−COO], 1.7−1.9 (m, 2 H, C*H*$_2$−CH_2−COO), 2.1 (s, 3 H, CH_3−COO), 2.3−2.4 (t, J = 7.0 Hz, 2 H, CH_2−COO), 2.8−2.9 [ddd, J = 6.4, 4.7, 2.2 Hz, 1 H, (CH_2)$_3$−C*H*−O], 2.9−3.0 (ddd, J = 6.2, 3.3, 2.2 Hz, 1 H, OCO−CH_2−C*H*−O), 3.6 (s, 3 H, CH_3O), 3.9 (dd, J = 12.2, 6.2 Hz, 1 H, 1 H of CH_2−OCO), 4.3 (dd, J = 12.2, 3.3 Hz, 1 H, 1 H of CH_2−OCO). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.5 (*C*H_3−CO), 21.1 (*C*H_2−CH_2−CO), 30.6 [*C*H_2−(CH_2)$_2$−CO], 33.2 (*C*H_2−COO), 51.4 (CH_3O), 54.9 (O−*C*H−CH_2−OCO), 55.9 [O−*C*H−(CH_2)$_3$], 64.4 (*C*H_2OCO), 170.6 (CH_3−*C*OO), 173.5 (*C*OOCH$_3$). − [*ee* >94% determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent in C_6D_6].

7-Acetoxy-(5*R*,6*R*)-epoxyheptanoic Acid Methyl Ester (17a): Following the same procedure as described for the preparation of compound **17**, compound **16a** was transformed to compound **17a**. − $[\alpha]_D^{20}$ = +35.6 (c = 0.23, $CHCl_3$).

(5*S*,6*S*)-Epoxy-7-hydroxyheptanoic Acid Methyl Ester (18): The acetate **17** (22.2 g, 0.10 mol) was dissolved in MeOH (200 mL) and Na_2SO_4 (15.0 g) was added. After stirring for 10 min K_2CO_3 (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 CH_2Cl_2 (300 mL) and washed with brine (50 mL). After drying over Na_2SO_4 and concentrating under reduced pressure the epoxy alcohol **18** (12.1 g, 69%) was obtained. − $[\alpha]_D^{20}$ = −34.0 (c = 1, CH_2Cl_2) {ref.[22] $[\alpha]_D^{20}$ = −35 (c = 2.7, $CHCl_3$)}. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.4−1.6 [m, 2 H, C*H*$_2$−(CH_2)$_2$−COO], 1.6−1.8 (m, 2 H, C*H*$_2$−CH_2−COO), 2.3 (t, J = 7.3 Hz, 2 H, CH_2−COO), 2.7−2.8 (br. s, 1 H, OH), 2.8−2.9 (m, 2 H, C*H*−O−C*H*), 3.5 (dd, J = 12.6, 4.5 Hz, 1 H, 1 H of CH_2−O), 3.6 (s, 3 H, CH_3O), 3.8 (dd, J = 12.6, 2.4 Hz, 1 H, 1 H of CH_2−O). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 21.1 (*C*H_2−CH_2−CO), 30.6 [*C*H_2−(CH_2)$_2$−CO], 33.2 (*C*H_2−CO), 51.3 (CH_3O), 55.3 (CH−O), 58.2 (CH−O), 61.6 (CH_2−O), 173.7 (CO).

(5*R*,6*R*)-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**. − $[\alpha]_D^{20}$ = + 33.6 (c = 0.14, $CHCl_3$).

(5*S*,6*R*)-Epoxy-6-formylhexanoic Acid Methyl Ester (5): To a flame-dried flask under Ar were added finely powdered 4 A molecular sieves (5.0 g) and the flask was flame dried again. Chromium(VI) oxide (33.4 g, 0.33 mol) and CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 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.

(5*S*,6*S*)-Epoxy-10-formyl-(7*E*,9*E*)-decadienoic Acid Methyl Ester (19): To the aldehyde **5** (7.0 g, 40.7 mmol) in CH_2Cl_2 (70 mL) was added dropwise a solution of phosphorane **6** (22.7 g, 68.7 mmol) in CH_2Cl_2 (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 SiO_2 was further washed with hexane/EtOAc (1:1) and the combined fractions were dried over Na_2SO_4. The solvent was evaporated under reduced pressure affording a mixture of *cis-trans* and *trans-trans* isomers.

The crude mixture was dissolved in CH_2Cl_2 (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 $Na_2S_2O_3$ (25 mL). The phases were separated, the organic layer was dried over Na_2SO_4 and concentrated under vacuo. The product was purified by flash chromatography (SiO_2, hexane/EtOAc 8:2) and the epoxy aldehyde **19** (4.5 g, 50%) was obtained as a pale-yellow solid. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.5−1.7 [m, 2 H, C*H*$_2$−(CH_2)$_2$−COO], 1.7−1.9 (m, 2 H, C*H*$_2$−CH_2−COO), 2.3−2.4 (t, J = 6.9 Hz, 2 H, CH_2−COO), 2.9 [ddd, J = 6.3, 4.8, 2.1 Hz, 1 H, O−C*H*−(CH_2)$_3$], 3.2 (dd, J = 7.2, 2.1 Hz, 1 H, O−C*H*−CH=), 3.6 (s, 3 H, CH_3O), 5.9−6.0 (dd, J = 15.3, 7.2 Hz, 1 H, C*H*=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, =C*H*−CH=CH−CO), 7.0−7.1 (ddd, J = 15.3, 11.1, 0.6 Hz, 1 H, C*H*=CH−CO), 9.5 (d, J = 7.8 Hz, 1 H, CHO). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 21.1 (*C*H_2−CH_2−CO), 31.1 [*C*H_2−(CH_2)$_2$−CO], 33.3 (*C*H_2−CO), 51.5 (CH_3), 57.0 (O−*C*H−CH=), 60.9 [O−*C*H−(CH_2)$_3$], 131.0 (=*C*H−CH=CH−CHO), 132.3 (=*C*H−CO), 141.1 (*C*H=CH−CH=CH−CO), 149.8 (*C*H=CH−CO), 173.6 (COO), 193.5 (CO).

LTA$_4$ 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/Et_2O/Et_3N 9:1:1 (250 mL; 0 °C) and washed with Na_2CO_3 solution (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuo affording crude **4**. Purification by flash chromatography [SiO_2, hexane/EtOAc 9:1 (10% Et_3N)] afforded LTA$_4$ methyl ester (**4**) (1.4 g, 63%). − $[\alpha]_D^{20}$ = −23.0 (c = 0.16, cyclohexane) {ref.[7] $[\alpha]_D^{20}$ = −21.9 (cyclohexane)}. − ^{1}H NMR (C_6D_6, 300 MHz): δ = 0.8 (t, J = 6.9 Hz, 3 H,

CH_3-CH_2), 1.1−1.2 [m, 4 H, $(CH_2)_2-CH_3$], 1.2−1.4 [m, 4 H, $CH_2-(CH_2)_2-COO$, $CH_2-(CH_2)_2-CH_3$], 1.5−1.6 (m, 2 H, CH_2-CH_2-COO), 1.9−2.0 [m, 2 H, $CH_2-(CH_2)_3-CH_3$], 2.0 (t, J = 7.5 Hz, 2 H, CH_2-COO), 2.5 [dt, J = 5.7, 1.8 Hz, 1 H, $O-CH-(CH_2)_3$], 2.8−3.0 (m, 3 H, $=CH-CH_2-CH=$, $O-CH-CH=$), 3.3 (s, 3 H, CH_3O), 5.2−5.3 (dd, J = 15.2, 7.8 Hz, 1 H, $=CH-CH-O$), 5.3−5.5 (m, 3 H, $=CH-CH_2-CH=CH$), 6.0 (m, 1 H, $=CH-CH=CH-CH_2$), 6.1 (dd, J = 14.9, 10.8 Hz, 1 H, $CH=CH-CH=CH-CH_2$), 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, $=CH-CH=CH-CH_2$). − ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 14.1 (CH_3-CH_2), 21.5 (CH_2-CH_2-CO), 22.8 (CH_2-CH_3), 26.5 ($=CH-CH_2-CH=$), 27.5 [$CH_2-(CH_2)_3-CH_3$], 29.6 (CH_2), 31.5 (CH_2), 31.7 ($CH_2-CH_2-CH_3$), 33.4 (CH_2-CO), 50.9 (CH_3-O), 57.8 ($O-CH-CH=$), 60.3 [$O-CH-(CH_2)_3$], 127.4 ($=CH-CH_2$), 128.8 ($=CH-CH=CH-CH_2$), 129.0 ($=CH-CH=CH-CH_2$), 131.1, 131.3, 131.4 ($=CH-CH-O$, 2 × $=CH-CH_2$), 132.2 ($CH=CH-CH=CH-CH_2$), 134.0 ($CH=CH-CH-O$), 172.9 (CO).

1-Acetoxy-(2*S*,3*S*)-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). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.9 (t, J = 6.9 Hz, 3 H, CH_3), 1.2−1.4 [m, 4 H, $(CH_2)_2-CH_3$], 1.4−1.6 [m, 4 H, $(CH_2)_2-(CH_2)_2-CH_3$], 2.1 (s, 3 H, CH_3-CO), 2.8−2.9 [dt, J = 5.6, 2.4 Hz, 1 H, $O-CH-(CH_2)_4$], 2.9−3.0 (ddd, J = 6.3, 3.3, 2.4 Hz, 1 H, $O-CH-CH_2-OAc$), 3.9 (dd, J = 12.3, 6.3 Hz, 1 H, 1 H of CH_2-OAc), 4.3−4.4 (dd, J = 12.3, 3.3 Hz, 1 H, 1 H of CH_2-OAc). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8 (CH_3-CH_2), 20.6 (CH_3-CO), 22.4 (CH_2-CH_3), 25.4 [$CH_2-(CH_2)_2-CH_3$], 31.4, 31.4 ($CH_2-CH_2-CH_2-CH_2-CH_3$), 55.2 ($O-CH-CH_2-OAc$), 56.6 [$O-CH-(CH_2)_4$], 64.7 (CH_2-OAc), 170.8 (CO). − [*ee* >94% determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent].

(2*S*,3*S*)-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. 38−39 °C (ref.[40] m.p. 38.0−39.5 °C). − $[\alpha]_D^{20}$ = −37.0 (c = 1, CH_2Cl_2) {ref.[47] $[\alpha]_D^{20}$ = −44 (c = 1.0, $CHCl_3$)}. −^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz): δ = 0.8 (t, J = 6.9 Hz, 3 H, CH_3), 1.1−1.3 [m, 4 H, $(CH_2)_2-CH_3$], 1.3−1.6 [m, 4 H, $(CH_2)_2-(CH_2)_2-CH_3$], 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 CH_2-OH), 3.8 (dd, J = 12.6, 2.4 Hz, 1 H, 1 H of CH_2-OH). − ^{13}C NMR ($CDCl_3$/CD_3OD, 75.5 MHz): δ = 13.7 (CH_3), 22.3 (CH_2-CH_3), 25.4 [$CH_2-(CH_2)_2-CH_3$], 31.4 (2 C, $CH_2-CH_2-CH_2-CH_2-CH_3$), 56.2 (CH−O), 58.7 (CH−O), 61.7 (CH_2-OH).

(2*R*,3*S*)-Epoxyoctanal (22): To a flame-dried flask under Ar were added finely powdered 4 A 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%). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.9 (t, J = 7.0 Hz, 3 H, CH_3), 1.2−1.4 [m, 4 H, $(CH_2)_2-CH_3$], 1.4−1.6 [m, 2 H, $CH_2-(CH_2)_2-CH_3$], 1.6−1.7 [m, 2 H, $CH_2-(CH_2)_3-CH_3$], 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): δ = 13.7 (CH_3), 22.3 (CH_2-CH_3), 25.3 [$CH_2-(CH_2)_2-CH_3$], 31.1 (CH_2), 31.3 (CH_2), 56.7 ($O-CH-CH_2$), 59.1 ($O-CH-CHO$), 198.4 (CHO).

(6*S*,7*S*)-Epoxy-(2*E*,4*E*)-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 $Na_2S_2O_3$ (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, $CHCl_3$)}. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.9 (t, J = 6.9 Hz, 3 H, CH_3), 1.2−1.8 [m, 8 H, $(CH_2)_4$], 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, $=CH-CH-O$), 6.2 (dd, J = 15.3, 7.8 Hz, 1 H, $=CH-CHO$), 6.6 (dd, J = 15.3, 10.8 Hz, 1 H, $=CH-CH=CH-CHO$), 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): δ = 13.8 (CH_3), 22.4 (CH_2-CH_3), 25.4 [$CH_2-(CH_2)_2-CH_3$], 31.4 (CH_2), 31.8 (CH_2), 57.3 ($O-CH-CH=$), 61.6 ($O-CH-CH_2$), 130.7 ($=CH-CH=CH-CHO$), 132.2 ($=CH-CHO$), 141.6 ($O-CH-CH=$), 150.1 ($CH=CH-CHO$), 193.7 (CHO).

(14*S*,15*S*)-LTA$_4$ 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*)-LTA$_4$ methyl ester (**24**) (0.14 g, 63%). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.9 (t, J = 6.9 Hz, 3 H, CH_3), 1.1−1.5 [m, 6 H, $(CH_2)_3-CH_3$], 1.5−1.6 [m, 2 H, $CH_2-(CH_2)_3-CH_3$], 1.6−1.7 (m, 2 H, CH_2-CH_2-COO), 2.0−2.2 [m, 2 H, $CH_2-(CH_2)_2-COO$], 2.3 (t, J = 7.5 Hz, 2 H, CH_2-COO), 2.7−3.0 [m, 3 H, $=CH-CH_2-CH=$, $O-CH-(CH_2)_4$], 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, $=CH-CH_2-CH=CH-CH_2$, $=CH-CH-O$), 6.0 (br. t, J = 11.3 Hz, 1 H, $CH_2-CH=CH-CH=$), 6.2 (dd, J = 15.0, 10.8 Hz, 1 H, $=CH-CH=CH-CH-O$), 6.4−6.6 (m, 2 H, $CH=CH-CH-O$, $CH=CH-CH=CH-CH-O$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8 (CH_3), 22.4 (CH_2-CH_3), 24.6 (CH_2-CH_2-COO), 25.4

[$CH_2-(CH_2)_2-CH_3$], 26.0 (=CH−CH_2−CH=), 26.4 [$CH_2-(CH_2)_2-COO$], 31.4 ($CH_2-CH_2-CH_3$), 31.9 [$CH_2-(CH_2)_3-CH_3$], 33.2 (CH_2-COO), 51.3 (CH_3O), 58.4 (O−CH−CH=), 61.1 (O−CH−CH_2), 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-LTA$_4$ 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/Et_2O/Et_3N 9:1:1. The crude reaction mixture was washed with a $NaHCO_3$ solution and the organic layer was dried over Na_2SO_4 and concentrated under vacuo affording crude **28**. Purification by flash chromatography [SiO_2, hexane/EtOAc 9:1 (10% Et_3N)] afforded [$^2H_2$]-LTA$_4$ methyl ester (**28**) (0.13 g, 58%). − ^{1}H NMR (C_6D_6, 300 MHz): δ = 0.8−0.9 (t, *J* = 6.9 Hz, 3 H, CH_3-CH_2), 1.1−1.4 [m, 8 H, $CH_2-(CH_2)_2-COO$, $(CH_2)_3-CH_3$], 1.5−1.6 (m, 2 H, CH_2-CH_2-COO), 1.8−2.0 [m, 2 H, $CH_2-(CH_2)_3-CH_3$], 2.0 (t, *J* = 7.2 Hz, 2 H, CH_2-COO), 2.5 [dt, *J* = 5.6, 2.0 Hz, 1 H, O−CH−$(CH_2)_3$], 2.8−2.9 (m, 3 H, =CH−CH_2−CH=, O−CH−CH=), 3.3 (s, 3 H, CH_3O), 5.2−5.3 (dd, *J* = 15.2, 7.8 Hz, 1 H, =CH−CH−O), 5.3−5.5 (m, 1 H, =CH−CH_2−CH=), 6.0 (t, *J* = 11.1 Hz, 1 H, =CH−CH=CH−CH_2), 6.1 (dd, *J* = 14.7, 10.7 Hz, 1 H, CH=CH−CH=CH−CH_2), 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−CH_2). − ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 14.0 (CH_3-CH_2), 21.4 (CH_2-CH_2-CO), 22.7 (CH_2-CH_3), 26.3 (=CH−CH_2−CH=), 27.3 [$CH_2-(CH_2)_3-CH_3$], 29.5 (CH_2), 31.4 (CH_2), 31.6 ($CH_2-CH_2-CH_3$), 33.3 (CH_2-CO), 50.8 (CH_3O), 57.8 (O−CH−CH=), 60.2 (O−CH−CH_2), 127.0 (t, *J* = 24 Hz, CD=), 128.8 (=CH−CH=CH−CH_2), 129.0 (=CH−CH=CH−CH_2), 130.6 (t, *J* = 24 Hz, CD=), 131.3, 131.5 (=CH−CH−O, =CH−CH_2), 132.2 (CH=CH−CH=CH−CH_2), 134.0 (CH=CH−CH−O), 172.9 (CO).

LTC$_4$ Mono Methyl Ester (29): LTA$_4$ methyl ester (**4**) (40.0 mg, 0.12 mmol) was stirred under argon with glutathione (70.0 mg, 0.23 mmol) in MeOH/Et_3N (3:1, 2 mL) for 12 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography [SiO_2, step gradient from EtOAc (10% Et_3N) to MeOH] affording LTC$_4$ monomethyl ester (**29**) (42.5 mg, 55%). − UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. − ^{1}H NMR (CD_3OD, 300 MHz): δ = 0.9 (t, *J* = 6.9 Hz, 3 H, CH_3-CH_2), 1.2−1.4 [m, 8 H, $CH_2-CH-OH$, $(CH_2)_3-CH_3$], 1.5−1.9 (m, 2 H, $CH_2-CH_2-COOCH_3$), 2.0−2.2 [m, 4 H, $CH_2-CH-NH_2$, $CH_2-(CH_2)_3-CH_3$], 2.3 (t, *J* = 7.2 Hz, 2 H, $CH_2-COOCH_3$), 2.5−2.6 (m, 2 H, $CH_2-CO-NH$), 2.6−2.8 (dd, *J* = 13.8, 9.6 Hz, 1 H, 1 H of CH_2-S), 2.8−3.0 (m, 3 H, =CH−CH_2−CH=, 1 H of CH_2-S), 3.3−3.4 (dd, *J* = 10.1, 4.1 Hz, 1 H, CH−S), 3.6 (s, 3 H, CH_3O), 3.6−3.7 (m, 2 H, CH−OH, $CH-NH_2$), 3.8 (2 d AB system, *J* = 17.0 Hz, 2 H, NH−CH_2−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−CH_2−CH=CH−CH_2), 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−CH_2), 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−CH_2). − ^{13}C NMR (CD_3OD, 75.5 MHz): δ = 14.4 (CH_3-CH_2), 22.4 ($CH_2-CH_2-COOCH_3$), 23.6 (CH_2-CH_3), 27.1 (=CH−CH_2−CH=), 27.8 ($CH_2-CH-NH_2$), 28.1 [$CH_2-(CH_2)_3-CH_3$], 30.4 [$CH_2-(CH_2)_2-CH_3$], 32.6 ($CH_2-CH_2-CH_3$), 33.2 ($CH_2-CH_2-CH-NH_2$), 34.6 [$CH_2-COOCH_3$, $CH_2-CH-OH$ (ambiguity remains)], 35.6 (CH_2-S), 43.5 ($NH-CH_2-COO$), 52.0 (CH_3-O), 54.5 (CH−NH−CO), 55.6 ($CH-NH_2$), 55.7 (CH−S), 74.1 (CH−OH), 128.5 (=CH−CH_2), 129.3 (=CH−CH=CH−CH_2), 129.8 (=CH−CH=CH−CH_2), 131.6 (=CH−CH−S), 131.7 (2 C, 2 × =CH−CH_2), 133.5 (CH=CH−CH=CH−CH_2), 134.8 (CH=CH−CH−S), 172.9, 174.1, 174.7, 175.6, 176.0 (5 CO).

LTC$_4$ (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 K_2CO_3 (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 NH_4OAc (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 H_2O (5 mL). The product in H_2O (0.2−0.3 mL) was absorbed on the Sep−Pak cartridge. The cartridge was washed with H_2O (5 mL) and the product was eluted with H_2O/MeOH (1:1, 5 mL), H_2O/MeOH (3:7, 5 mL) and MeOH (5 mL). The amount of LTC$_4$ (**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. − ^{1}H NMR (Fraction eluted from C_{18}-cartridge with H_2O/MeOH 3:7; CD_3OD, 300 MHz): δ = 0.9 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.2−1.4 [m, 6 H, $(CH_2)_3-CH_3$], 1.4−1.8 [m, 4 H, $(CH_2)_2-CH_2-COO$], 2.0−2.1 [m, 2 H, $CH_2-(CH_2)_3-CH_3$], 2.1−2.2 (m, 2 H, $CH_2-CH-NH_2$), 2.2−2.3 (t, *J* = 7.2 Hz, 2 H, CH_2-CH_2-COO), 2.5 (t, *J* = 7.1 Hz, 2 H, $CH_2-CO-NH$), 2.7 (dd, *J* = 14.0, 9.6 Hz, 1 H, 1 H of CH_2-S), 2.8−3.0 (m, 3 H, =CH−CH_2−CH=, 1 H of CH_2-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, $CH-NH_2$), 3.7 (2 d AB system, *J* = 17.1 Hz, 2 H, NH−CH_2−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−CH_2−CH=CH−CH_2), 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−CH_2), 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−CH_2). − ^{13}C NMR (CD_3OD, 75.5 MHz): δ = 14.4 (CH_3), 23.0 (CH_2-CH_2-COO), 23.6 (CH_2-CH_3), 27.1 (=CH−CH_2−CH=), 27.9, 28.1 [$CH_2-(CH_2)_3-CH_3$, $CH_2-CH-NH_2$], 30.4 [$CH_2-(CH_2)_2-CH_3$], 32.6 ($CH_2-CH_2-CH_3$), 33.2 ($CH_2-CH_2-CH-NH_2$), 35.9 (CH_2-S), 36.5 [CH_2-CH_2-COO, $CH_2-CH-OH$ (ambiguity remains)], 44.4 ($NH-CH_2-COO$), 54.4 (CH−NH−CO), 55.7 (2 C, CH−S, $CH-NH_2$), 74.2 (CH−OH), 128.5 (=CH−CH_2), 129.2 (=CH−CH=CH−CH_2), 129.8 (=CH−CH=CH−CH_2), 131.6, 131.7, 131.9 (2 × =CH−CH_2, =CH−CH−S), 133.6 (CH=CH−CH=CH−CH_2), 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-LTD$_4$ 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 LTA_4 methyl ester (**4**).

LTA_4 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/Et_3N (3:1, 2 mL) for 4 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography (SiO_2, hexane/EtOAc/Et_3N 80:20:10) affording **30** (71.7 mg, 77%). − UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.9 (t, *J* = 6.8 Hz, 3 H, *CH*$_3$−CH$_2$), 1.2−1.4 [m, 6 H, (*CH*$_2$)$_3$−CH$_3$], 1.4−1.9 [m, 4 H, (*CH*$_2$)$_2$−CH$_2$−COOCH$_3$], 2.3 (t, *J* = 7.1 Hz, 2 H, *CH*$_2$−COOCH$_3$), 2.6 (br. s, 1 H, OH), 2.7−3.1 (2 dd AB system, *J* = 14.3, 7.7 Hz, 2 H, CH$_2$−S), 2.9 (br. t, *J* = 7.8 Hz, 2 H, =CH−*CH*$_2$−CH=), 3.5 (dd, *J* = 9.9, 3.6 Hz, 1 H, CH−S), 3.6 (s, 3 H, CH$_3$O), 3.7−3.8 (m, 1 H, C*H*−OH), 3.8 (s, 3 H, CH$_3$O), 4.0−4.2 (2 dd AB system, *J* = 18.3, 5.1 Hz, *J* = 18.3, 5.4 Hz, 2 H, NH−*CH*$_2$−COO), 4.6−4.7 (m, 1 H, C*H*−NH), 5.3−5.5 (m, 3 H, =C*H*−CH$_2$−C*H*=C*H*−CH$_2$), 5.7 (dd, *J* = 14.7, 9.9 Hz, 1 H, =C*H*−CH−S), 6.0 (t, *J* = 11.4 Hz, 1 H, C*H*=CH−CH$_2$−CH=), 6.2 (d, *J* = 14.4, 10.8 Hz, 1 H, C*H*=CH−CH=CH−CH$_2$), 6.3 (dd, *J* = 14.7, 10.8 Hz, 1 H, C*H*=CH−CH−S), 6.5−6.6 (dd, *J* = 14.4, 11.4 Hz, 1 H, =C*H*−CH=CH−CH$_2$), 7.0 (t, *J* = 5.4 Hz, 1 H, N*H*−CH$_2$), 7.6 (br. d, *J* = 6.9 Hz, 1 H, NHCOCF$_3$). − ^{13}C NMR ($CDCl_3$, 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 *COCF*$_3$ were not observed due to the low intensity.

LTD_4 (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 K_2CO_3 (6.0 mL) was added. After 3.5 h the reaction was quenched by neutralization with glacial acetic acid (66 μL) in water (1 mL). Concentration under vacuo and purification through a reversed-phase cartridge (Sep−pak), as described for compound **1**, afforded LTD_4 (**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 $[M_{LTD4} - (Gly-cys) + H^+]^+$.

LTE_4 Dimethyl Ester (31): LTA_4 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/Et_3N (3:1, 2 mL) under argon for 5 h. The MeOH was evaporated under reduced pressure and the crude product purified by flash chromatography (SiO_2, hexane/EtOAc/Et_3N 50:50:10) affording **31** (70.1 mg, 75%). − UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. − ^{1}H NMR (C_6D_6, 300 MHz): δ = 1.0 (t, 3 H, *J* = 6.8 Hz, CH$_3$), 1.3−1.5 [m, 6 H, (*CH*$_2$)$_3$−CH$_3$], 1.5−1.7 (m, 2 H, C*H*$_2$−CH−OH), 1.7−2.1 (m, 2 H, C*H*$_2$−CH$_2$−COO), 2.1 (m, 2 H, =CH−C*H*$_2$−CH$_2$), 2.2 (t, *J* = 14.4 Hz, 2 H, C*H*$_2$−COOCH$_3$), 2.8 (dd AB system, *J* = 13.8, 6.6 Hz, 1 H, 1 H of CH$_2$−S), 2.9 (2 dd AB system, *J* = 13.8, 5.1 Hz, 1 H, 1 H of CH$_2$−S), 3.0 (br. t, *J* = 6.3 Hz, 2 H, =CH−C*H*$_2$−CH=), 3.4−3.5 (2 s, 6 H, 2 × CH$_3$O), 3.5−3.6 (m, 2 H, CH−S, C*H*−NH$_2$), 3.8 (dt, *J* = 9.0, 3.8 Hz, 1 H, C*H*−OH), 5.4−5.5 (m, 3 H, =C*H*−CH$_2$−C*H*=C*H*−CH$_2$), 5.9 (dd, *J* = 14.4, 9.6 Hz, 1 H, =C*H*−CH−S), 6.1 (t, *J* = 11.1 Hz, 1 H, =CH−C*H*=CH−CH$_2$), 6.1−6.3 (m, 2 H, =C*H*−C*H*=CH−CH−S), 6.6 (dd, *J* = 14.1, 11.1 Hz, 1 H, =C*H*−CH=CH−CH$_2$). − ^{13}C NMR (C_6D_6, 75.5 MHz): δ = 14.0 (*CH*$_3$−CH$_2$), 21.7 (*CH*$_2$−CH$_2$−COO), 22.7 (*CH*$_2$−CH$_3$), 26.4 (=CH−*CH*$_2$−CH=), 27.4 [*CH*$_2$−(CH$_2$)$_3$−CH$_3$], 29.5 [*CH*$_2$−(CH$_2$)$_2$−CH$_3$], 31.6 (*CH*$_2$−CH$_2$−CH$_3$), 33.7 (*CH*$_2$−COO), 34.3 (*CH*$_2$−CH−OH), 35.4 (CH$_2$−S), 50.8 (CH$_3$O), 51.5 (CH$_3$O), 54.7, 55.6 (CH−NH$_2$, CH−S), 72.9 (CH−OH), 127.6 (=*CH*−CH$_2$), 128.1 (*CH*=CH−CH=CH−CH−S), 129.1 (=CH−*CH*=CH−CH$_2$), 130.7 (=*CH*−CH−S), 131.0 (=*CH*−CH$_2$), 131.0 (=*CH*−CH$_2$), 132.7 (=*CH*−CH=CH−CH−S), 134.0 (*CH*=CH−CH−S), 173.5 (COO), 174.2 (COO).

LTE_4 (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 K_2CO_3 (4.0 mL) was added. After 3.5 h the reaction was quenched by neutralization with glacial acetic acid (44 μL) in water (1 mL). Concentration under vacuo and purification through a reversed-phase cartridge, as described for compound **1**, afforded LTE_4 (**3**) (54.4 mg, 82%). − UV (MeOH): λ_{max} = 271(sh), 281, 291(sh) nm. − API ES/MS (negative ionization mode): *m*/*z* (%) = 438 $[M_{LTE4} - H^+]^-$.

Acknowledgments

Financial support of this research in part by Laboratorios Lasa S.A., Barcelona (Spain), the Asthma Research Council, UK and the Department of Cell Biology UMDNJ-SOM is gratefully acknowledged. We would like to thank *Pharmacia&Upjohn* for kindly providing us with standards of leukotrienes for comparison.

[1] [1a] S. Bergstrom, *Science* **1967**, *157*, 382−391. − [1b] S. Bergstrom, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 858−866.
[2] [2a] J. S. Masferrer, K. Seibert, B. Zweifel, P. Needleman, *Proc. Nat. Acad. Sci. USA* **1992**, *89*, 3917−3921. − [2b] P. Needleman, P. C. Isakson, *J. Rheumatol.* **1997**, *24*, 6−8.
[3] [3a] B. Samuelsson, *Science* **1983**, *220*, 568−575. − [3b] B. Samuelsson, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 805−815.
[4] [4a] C. N. Serhan, M. Hamberg, B. Samuelsson, *Proc. Nat. Acad. Sci. USA* **1984**, *81*, 5335−5339. − [4b] B. Samuelsson, S. E. Dahlen, J. A. Lindgren, C. A. Rouzer, C. N. Serhan, *Science* **1987**, *237*, 1171−1176. − [4c] T. H. Lee, A. E. G. Crea, V. Gant, B. W. Spur, B. E. Marron, K. C. Nicolaou, E. Reardon, M. Brezinski, C. N. Serhan, *Am. Rev. Resp. Dis.* **1990**, *141*, 1453−1458.
[5] W. Feldberg, C. H. Kellaway, *J. Physiol.* (London) **1938**, *94*, 187−226.
[6] [6a] R. P. Orange, M. D. Valentine, K. F. Austen, *Science* **1967**, *157*, 318−319. − [6b] R. P. Orange, D. J. Stechschulte, K. F. Austen, *J. Immunol.* **1970**, *105*, 1087−1095. − [6c] R. P. Orange, R. C. Murphy, M. L. Karnovsky, K. F. Austen, *J. Immunol.* **1973**, *110*, 760−770.
[7] E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, S. Hammarstrom, *J. Am. Chem. Soc.* **1980**, *102*, 1436−1438.
[8] [8a] E. J. Corey, G. Goto, *Tetrahedron Lett.* **1980**, *21*, 3463−3466. − [8b] E. J. Corey, D. A. Clark, A. Marfat, G. Goto, *Tetrahedron Lett.* **1980**, *21*, 3143−3146.
[9] [9a] R. A. Lewis, K. F. Austen, R. J. Soberman, *N. Engl. J. Med.* **1990**, *323(10)*, 645−655. − [9b] J. M. Drazen, E. Israel, P. M. O'Byrne, *N. Engl. J. Med.* **1999**, *340*(3), 197−206.
[10] A. W. Ford-Hutchinson, *Crit. Rev. Immunol.* **1990**, *10*, 1−12.
[11] J. Gosselin, P. Borgeat, *United States Patent* 5,789,441 (Virocell Inc.) **1998**.
[12] [12a] B. W. Spur, A. Crea, W. Peters, W. Konig, *Arch. Pharm.* (Weinheim) **1985**, *318*, 225−228. − [12b] Y. Hanzawa, K. Kawagoe, K. Inazawa, Y. Kobayashi, *Tetrahedron Lett.* **1988**, *29*, 5665−5666. − [12c] Y. Tanaka, T. M. Klauck, W. Jubiz, T. Taguchi, Y. Hanzawa, A. Igarashi, K. Inazawa, Y. Kobayashi, R. G. Briggs. *Arch. Biochem. Biophys.* **1988**, *263*, 178−190.
[13] [13a] T. H Lee, J. P. Arm, B. W. Spur, *Leukotrienes and bronchial hyperreactivity. In, Allergy and Inflammation* (Ed.: A. B. Kay), Blackwell Scientific Publ., **1987**, 245−259. − [13b] J. P. Arm, B. W. Spur, T. H. Lee, *J. Allergy Clin. Immunol.* **1988**, *82*, 654−660. − [13c] S. P. O'Hickey, J. P. Arm, P. J. Rees, B. W. Spur, T. H. Lee, *Eur. Resp. J.* **1988**, *1*, 913−917. − [13d] J. P.

Arm, S. P. O'Hickey, B. W. Spur, T. H. Lee, *Am. Rev. Resp. Dis.* **1989**, *140*, 148−153. − [13e] J. P. Arm, S. P. O'Hickey, R. J. Hawksworth, C. Y. Fong, A. E. G. Crea, B. W. Spur, T. H. Lee, *Am. Rev. Respir. Dis.* **1990**, *142*, 1112−1118.− [13f] S. P. O'Hickey, R. J. Hawksworth, C. Y. Fong, J. P. Arm, B. W. Spur, T. H. Lee, *Am. Rev. Resp. Dis.* **1991**, *144* (5), 1053−1057. − [13g] P. E. Christie, R. Hawksworth, B. W. Spur, T. H. Lee, *Am. Rev. Respir. Dis.* **1992**, *146*, 1506−1510.− [13h] L. A. Laitinen, A. Laitinen, T. Haahtela, V. Vilkka, B. W. Spur, T. H. Lee, *Lancet* **1993**, *341*(8851), 989.

[14] [14a] E. J. Corey, J. R. Cashman, S. S. Kantner, S. W. Wright, *J. Am. Chem. Soc.* **1984**, *106*, 1503−1504. − [14b] B. W. Spur, A. Crea, W. Peters, W. Konig, *Arch. Pharm*. (Weinheim) **1984**, *317*, 84−86. − [14c] P. E. Christie, B. W. Spur, T. H. Lee, *J. Allergy Clin. Immunol*. **1991**, *88*(2), 193−198. − [14d] P. E. Christie, B. W. Spur, T. H. Lee, *Am. Rev. Respir. Dis.* **1992**, *145*, 1281−1284. − [14e] A. Markham, D. Faulds, *Drugs* **1998**, *56(2)*, 251−257.

[15] [15a] B. W. Spur, A. Crea, W. Peters, W. Konig, *Tetrahedron Lett*. **1983**, *24*, 2135−2136. − [15b] F. F. Sun, L. Y. Chau, B. W. Spur, E. J. Corey, R. A. Lewis, K. F. Austen, *J. Biol. Chem*. **1986**, *261*(18), 8540−8546. − [15c] R. J. Soberman, R. T. Okita, B. Fitzsimmons, J. Rokach, B. W. Spur, K. F. Austen, *J. Biol. Chem*. **1987**, *262*, 12421−12427. − [15d] T. Yoshimoto, R. J. Soberman, B. W. Spur, K. F. Austen, *J. Clin. Invest*. **1988**, *81*, 866−871.

[16] [16a] E. J. Corey, S. G. Pyne, W.-G. Su, *Tetrahedron Lett*. **1983**, *24*, 4883−4886. − [16b] B. W. Spur, A. Crea, W. Peters, W. Konig, *Arch. Pharm*. (Weinheim) **1984**, *317*, 280−281. − [16c] K. C. Nicolaou, S. E. Webber, J. Y. Ramphal, J. Abe, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1019−1021. − [16d] T. H. Lee, R. L. Hoover, J. D. Williams, R. L. Sperling, J. Ravalese, B. W. Spur, D. R. Robinson, E. J. Corey, R. A. Lewis, K. F. Austen, *New Engl. J. Med*. **1985**, *312* (19), 1217−1224. − [16e] R. I. Sperling, M. Weinblatt, J. L. Robin, J. Ravalese, R. L. Hoover, J. S. Coblyn, P. A. Fraser, B. W. Spur, D. R. Robinson, R. A. Lewis, K. F. Austen, *Arthritis Rheumatology* **1987**, *30*(9), 988−997. − [16f] B. W. Spur, C. Jacques, A. E. G. Crea, T. H. Lee, *Adv. Exp. Med. Biol*. **1988**, *229*, 147−154. − [16g] J. P. Arm, C. E. Horton, J.-M. Mencia-Huerta, F. House, N. M. Eiser, T. J. H. Clark, B. W. Spur, T. H. Lee, *Thorax* **1988**, *43*, 84−92. − [16h] T. H. Lee, T. Sethi, A. E. G. Crea, W. Peters, J. P. Arm, C. E. Horton, M. J. Walport, B. W. Spur, *Clin. Sci*. **1988**, *74*, 467−475. − [16i] J. P. Arm, C. E. Horton, B. W. Spur, J.-M. Mencia-Huerta, T. H. Lee, *Am. Rev. Resp. Dis.* **1989**, *139*, 1395−1400.

[17] A. Rodrıguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett*. **1999**, *40*, 5161−5164.

[18] R. H. Wollenberg, *Tetrahedron Lett*. **1978**, *19*, 717−720.

[19] E. J. Corey, J. O. Albright, *J. Org. Chem*. **1983**, *48*, 2114−2115.

[20] R. H. Green, P. F. Lambeth, *Tetrahedron* **1983**, *39*, 1687−1721.

[21] [21a] N. Cohen, B. L. Banner, R. J. Lopresti, *Tetrahedron Lett*. **1980**, *21*, 4163−4166. − [21b] N. Cohen, B. L. Banner, R. J. Lopresti, F. Wong, M. Rosenberger, Y.-Y Liu, E. Thom, A. A. Liebman, *J. Am. Chem. Soc.* **1983**, *105*, 3661−3672.

[22] [22a] J. Rokach, R. Zamboni, C.-K. Lau, Y. Guindon, *Tetrahedron Lett*. **1981**, *22*, 2759−2762. − [22b] P. Prasit, G. Robertson, J. Rokach, *Carbohydr. Res.* **1990**, *202*, 93−104.

[23] D. P. Marriott, J. R. Bantick, *Tetrahedron Lett*. **1981**, *22*, 3657−3658.

[24] S. R. Baker, D. W. Clissold, A. McKillop, *Tetrahedron Lett*. **1988**, *29*, 991−994.

[25] J. Rokach, R. Zamboni, C. K. Lau, Y. Guindon, *Tetrahedron Lett*. **1981**, *22*, 2763−2766.

[26] H. Maehr, A. Perrotta, J. Smallheer, *J. Org. Chem*. **1988**, *53*, 832−836.

[27] [27a] J. Rokach, R. N. Young, M. Kakushima, C.-K. Lau, R. Seguin, R. Frenette, R. Guindon, *Tetrahedron Lett*. **1981**, *22*, 979−982. − [27b] Y. Wang, J. Li, Y. Wu, Y. Huang, L. Shi, J. Yang, *Tetrahedron Lett*. **1986**, *27*, 4583−4584. − [27c] Y. Kobayashi, Y. Kitano, T. Matsumoto, F. Sato, *Tetrahedron Lett*. **1986**, *27*, 4775−4778.

[28] B. E. Rossiter, T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 464−465.

[29] E. J. Corey, S. Hashimoto, A. E. Barton, *J. Am. Chem. Soc*. **1981**, *103*, 721−722.

[30] [30a] G. A. Tolstikov, M. S. Miftakhov, A. G. Tolstikov, E. T. Lesnikova, *Zh. Org. Khim*. **1983**, *19*, 463. − [30b] M. S. Miftakhov, A. G. Tolstikov, G. A. Tolstikov, *Zh. Org. Khim*. **1984**, *20*, 678−683.

[31] J. W. Patterson, *Synthesis* **1985**, 337−339.

[32] [32a] J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley & Sons, New York, **1995**. − [32b] J. Tsuji, *Synthesis* **1990**, 739−749. − [32c] H. M. Colquhoun, *Chemistry and Industry* **1987**, 612−617.

[33] B. Driessen-Holscher, W. Keim, T. Prinz, H. J. Traenckner, J. D. Jentsch, *United States Patent* 5,834,611 (Bayer AG) **1998**, and references cited within.

[34] [34a] E. Monflier, P. Bourdauducq, J.-L. Couturier, J. Kervennal, A. Mortreux, *J. Mol. Catal. A: Chem.* **1995**, *97*, 29−33. − [34b] E. Monflier, P. Bourdauducq, J.-L. Couturier, J. Kervennal, A. Mortreux, *Applied Catal. A: General* **1995**, *131*, 167−178. − [34c] W. E. Walker, R. M. Manyik, K. E. Atkins, M. L. Farmer, *Tetrahedron Lett*. **1970**, *10*, 3817−3820. − [34d] S. Takahashi, T. Shibano, N. Hagihara, *Tetrahedron Lett*. **1967**, *7*, 2451−2453.

[35] D. Rose, H. Lepper, *J. Organomet. Chem*. **1973**, *49*, 473−476.

[36] J. Tsuji, H. Yasuda, T. Mandai, *J. Org. Chem*. **1978**, *43*, 3606−3607.

[37] A. Behr, G. v. Ilsemann, W. Keim, C. Kruger, Y.-H. Tsay, *Organometallics* **1986**, *5*, 514−518.

[38] R. M. Hanson, K. B. Sharpless, *J. Org. Chem*. **1986**, *51*, 1922−1925.

[39] J. G. Hill, K. B. Sharpless, C. M. Exon, R. Regenye, *Org. Synth*. **1985**, *63*, 66−78.

[40] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc*. **1987**, *109*, 5765−5780.

[41] A. Rodrıguez, M. Nomen, B. W. Spur, J. J. Godfroid, T. H. Lee, *Tetrahedron Lett*. **2000**, *41*, 823−826.

[42] I. Ernest, A. J. Main, R. Menasse, *Tetrahedron Lett*. **1982**, *23*, 167−170.

[43] [43a] M. Sugiura, H. Beierbeck, G. Kotovych, P. C. Belanger, *Can. J. Chem*. **1984**, *62*, 1640−1645. − [43b] P. Loftus, P. R. Bernstein, *J. Org. Chem*. **1983**, *48*, 40−44. − [43c] E. J. Corey, P. B. Hopkins, A. E. Barton, B. Bangerter, *Tetrahedron* **1982**, *38*, 2653−2657.

[44] R. L. Maas, A. L. Brash, J. A. Oates, *Proc. Nat. Acad. Sci. USA*, **1981**, *78*, 5523−5527.

[45] E. J. Corey, F. J. Zhang, *Org. Lett*. **1999**, *1* (8), 1287−1290.

[46] S. Tsuboi, H. Furutani, A. Takeda, *Bull. Chem. Soc. Jpn*. **1987**, *60*, 833−835.

[47] R. Zamboni, S. Milette, J. Rokach, *Tetrahedron Lett*. **1983**, *24*, 4899−4902.

[48] [48a] J. P. Lellouche, J. Deschamps, C. Boullais, J. P. Beaucourt, *Tetrahedron Lett*. **1988**, *29*, 3073−3076. − [48b] D. Delorme, Y. Girard, J. Rokach, *J. Org. Chem*. **1989**, *54*, 3635−3640. − [48c] M. L. Belley, Y. Gareau, R. J. Zamboni, D. G. Ahern, Y. Hong, *J. Labelled Comp. Radiopharm*. **1995**, *36*, 599−610.

[49] S. Hammarstrom, B. Samuelsson, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, E. J. Corey, *Biochem. Biophys. Res. Commun.* **1980**, *92*, 946−953.

[50] E. J. Corey, A. Marfat, G. Goto, F. Brion, *J. Am. Chem. Soc.* **1980**, *102*, 7984−7985.

[51] [51a] A. M. Kornilov, M. V. Furmanova, A. E. Sorochinskii, V. P. Kukhar, *Zh. Org. Khim*. **1992**, *28*, 1360−1363. − [51b] J. M. Palazon, B. Anorbe, V. S. Martın, *Tetrahedron Lett*. **1986**, *27*, 4987−4990. − [51c] M. Caron, K. B. Sharpless, *J. Org. Chem*. **1985**, *50*, 1557−1560.

Received March 30, 2000
[O00173]