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New Synthesis of Leukotriene B_3 Methyl Ester from bis(Trimethylsilyl) Unsaturated Derivatives

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Abstract: A new synthesis of leukotriene B_3 methyl ester is reported, starting from bis(trimethylsilyl) unsaturated derivatives as building blocks for the triene moiety of the leukotriene. The two stereogenic centers have been generated by enantioselective chemical reduction of two acetylenic ketones with both *R*- or *S*-Alpine Borane®. The three conjugated double bonds system of the leukotriene has been assembled by Miyaura-Suzuki cross-coupling reaction. © 1998 Elsevier Science Ltd. All rights reserved.

Leukotrienes represent the most interesting products of the metabolism of the arachidonic acid *via* the 5-lipoxygenase pathway.[1] The chief compound of this family, leukotriene B_4 (LTB_4), exhibits a strong chemotactic effect and is considered an important mediator of inflammatory processes.[2] Leukotriene B_3 (LTB_3) is an analogue of LTB_4, lacking in the non conjugated double bond. However, the biological activity of these molecules appears to be related to the specific configuration of both the conjugated double bond system and the two stereogenic centers. These two requirements are the same in the two leukotrienes, and actually the potency of LTB_3 has been demonstrated to be only marginally less than that of LTB_4.[3]

Owing to the restricted quantity of these products recoverable from natural sources, various synthetic methods have been developed mainly for LTB_4.[4] Only few works have been published concerning LTB_3 and some structural derivatives.[5] A few reported methods are valid for the synthesis of both compounds.[4a,b] The crucial points of a synthetic strategy for these biomolecules are represented by the construction of the conjugate triene system and by the creation of the two stereogenic centers with the appropriate configuration. Various solutions for these problems have been proposed in the literature and, among all, Wittig olefination,[4h-5a,b] Miyaura-Suzuki cross-coupling,[4b] or coupling of the appropriate acetylenic compound with a vinyl halide[4c,e-g] have been employed for the synthesis of the conjugated system. Enzymatic[4a,f] or chemical[4b,d,g-5a] kinetic resolution, enzymatic reduction of carbonyl compounds,[4f] or transformation of optically active compounds deriving from the chiral pool[4c,e-5a] have been worked out for the formation of the two stereogenic centers.

In our recent studies on the synthesis of stereodefined compounds[6] we have devised new methodologies[6a,e,g] for the synthesis of a series of natural compounds with a conjugated polyenyl structure,

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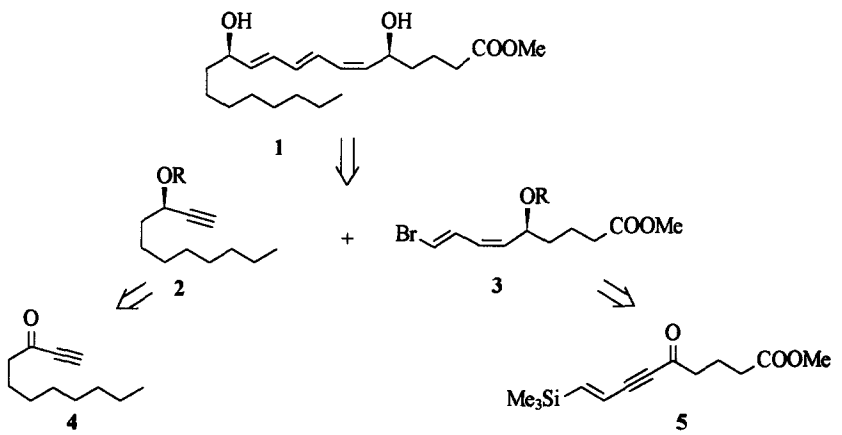
starting from unsaturated silyl derivatives. In particular, besides the (6*E*) isomer of LTB_3[6b], also a potential LTB_4 antagonist, SM-9064,[6d] and benzoleukotriene B_3,[6f] a leukotriene B_4 analogue, were prepared in an optically inactive form by means of our procedures.

Now we wish to report a new synthetic approach to chiral LTB_3 methyl ester **1**. Our overall synthesis design is summarized in a retroanalytical fashion in Scheme 1.

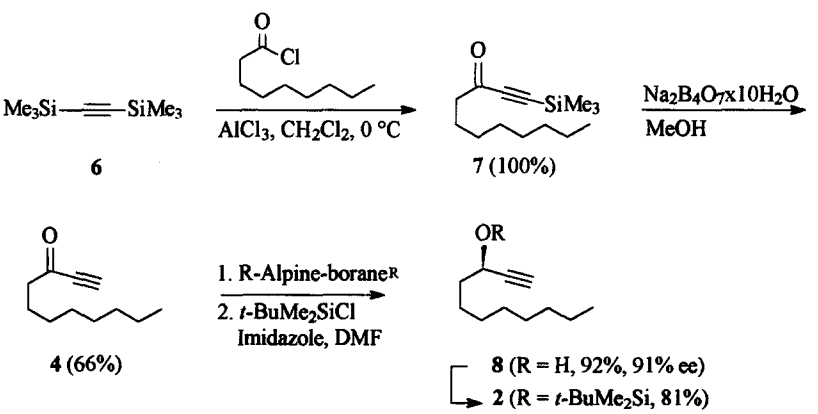
Thus, the disconnection of the C_9-C_{10} bond leads to the chiral fragments **2** and **3**, whose stereogenic centers can be respectively obtained by enantioselective chemical reduction of the acetylenic carbonyl compounds **4** and **5**. The key step leading to compound **1** requires a coupling reaction between the two fragments **2** and **3.**

Scheme 1



Accordingly, the synthesis of compound **2** was based upon the chemoselective acylation reaction of bis(trimethylsilyl)acetylene **6** with the nonanoyl chloride/$AlCl_3$ complex to give the acetylenic ketone **7** in quantitative yield (Scheme 2).

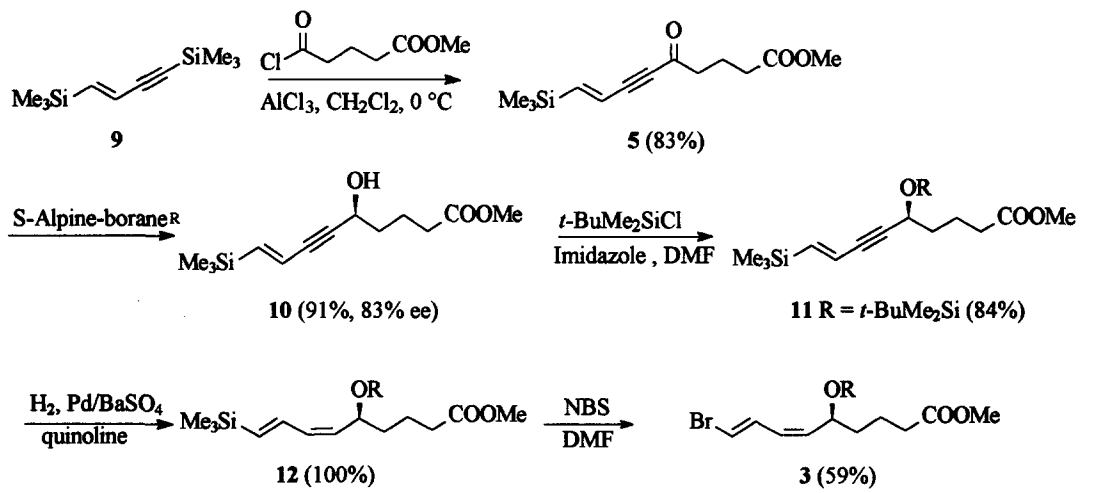
Scheme 2



The subsequent step required a simple desilylation reaction of compound **7** with borax (0.01 M) in methanol,[7] followed by the enantioselective reduction[8] of ketone **4** with *R*-Alpine-Borane^R in THF. The *R* propargylic alcohol **8** (91% e.e.) was obtained in 92% yield. Finally the protection of the alcoholic function of **8** completed the sequence leading to compound **2** in 81% yield.

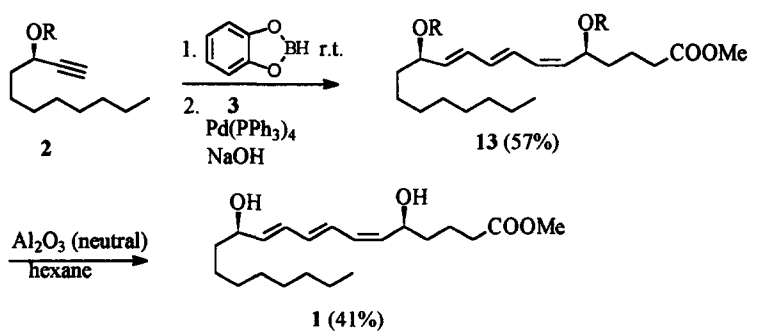
In the case of the dienic fragment **3** (Scheme 3), the *S* stereogenic center at C_5 [9] in compound **10** was generated in 83% e.e. by enantioselective chemical reduction with *S*-Alpine-Borane^R of the unsaturated ketone **5**, deriving from chemoselective acylation reaction of bis(trimethylsilyl) enyne **9**.[10] The *Z* configuration at C_6-C_7 double bond in compound **12** was obtained by catalytic hydrogenation of the triple bond of protected alcohol **11**. Finally, the sequence was completed by bromination reaction[11] of **12**, affording the compound **3** with the same configuration at the terminal double bond.

Scheme 3



The completion of the synthetic strategy described in Scheme 1 required a coupling reaction of the fragments **2** and **3** which was performed by a Miyaura-Suzuki cross-coupling procedure (scheme 4).[4b,12]

Scheme 4



Indeed, hydroboration of **2** with cathecolborane and subsequent cross-coupling reaction of the deriving, not isolated, vinylic boronic ester with **3** led to compound **13** in 57% yield. LTB_3 methyl ester **1** was obtained in 41% yield after appropriate deprotection reaction of **13** with neutral activated Al_2O_3.

In conclusion, we believe that our synthetic approach to LTB_3 compares favourably with other synthetic procedures as far as number of steps and chemical yields. A special advantage of our strategy is represented by the possibility of creating *both* stereogenic centers by reduction of two acetylenic ketones by the same chiral reagent used in both opposite configurations. In turn, the two ketones were easily obtained by acylation reaction of readily available unsaturated bis-trimethylsilyl derivatives, thus widening the synthetic potential of similar compounds.[6]

EXPERIMENTAL

Macherey-Nagel silica gel (60, particle size 0.040-0.063 mm) for flash chromatography and Macherey-Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC/mass-spectrometry analysis was performed on a Hewlett-Packard 5890 gas-chromatograph equipped with a HP-1 capillary column and HP MSD 5970B mass selective detector. ^{1}H-NMR spectra were recorded on a Brucker AM 500 spectrometer at 500 MHz and on a Varian XL 200 spectrometer at 200 MHz. *(R)*- and *(S)*-Alpine Borane^R (0.5 M solution in THF) were purchased from Aldrich. Commercial grade reagents and solvents were used as supplied with the following exceptions: methylene chloride, distilled over phosphorus pentoxide; benzene and THF over sodium-benzophenone ketyl; dimethylformamide over 4 Å molecular sieves. Reactions sensitives to oxygen and moisture were conducted under a nitrogen atmosphere. Enantiomeric excesses were evaluated by ^{1}H-NMR spectroscopy with the chiral shift reagent Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] Eu(hfc)$_3$, and/or by HPLC chromatography on a Chiralcel OD (Daicel) column.

1-Trimethylsilyl-1-undecyn-3-one (7). The nonanoyl chloride/$AlCl_3$ complex, obtained adding dropwise a solution of nonanoyl chloride (4.60 g, 26.03 mmol) in CH_2Cl_2 (15 mL) to a stirred suspension of $AlCl_3$ (3.57 g, 26.8 mmol) in CH_2Cl_2 (10 mL) at 0 °C under a nitrogen atmosphere, was added to a solution of bis(trimethylsilyl)acetylene (4.00 g, 23.47 mmol) in CH_2Cl_2 (35 mL) at 0 °C (1h reaction time). The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL), the organic phase separated and the aqueous phase extracted with CH_2Cl_2 (2 x 30 mL). The organic phases were washed with water, dried over anhydrous sodium sulfate, and the solvent removed at reduced pressure. The crude product was purified by distillation with a Kugelrohr apparatus (o.t. 125 °C, 3.2×10^{-4} mbar). A colourless oil (5.60 g) was obtained (100% yield). GC/MS (70 eV) 181(5), 165(7), 140(58), 125(100), 99(11), 97(34), 83(20), 75(39), 73(36), 55(22), 43(34), 41(32); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.23 (s, 9H), 0.87 (bt, J = 6.6 Hz, 3H), 1.18-1.36 (m, 10H), 1.58-1.74 (m, 2H), 2.54 (t, J = 7.4 Hz, 2H) ppm.

1-Undecyn-3-one (4). An aqueous solution of borax (0.01 M, 26 mL, 0.26 mmol) was added dropwise to a stirred solution of **7** (3.93 g, 16.47 mmol) in methanol (110 mL). The reaction was monitored by GC and TLC until the disappearance of the starting silyl ketone (15 min reaction time). Then the reaction mixture was cooled to 0 °C and acidified with aqueous HCl (1.2 M). The methanol was evaporated at reduced pressure and the residue extracted with ethyl acetate (3 x 50 mL). The organic phase was dried and concentrated. The crude product was purified by Kugelrohr distillation (o.t. 100 °C, 0.4 mbar). A colourless oil was obtained (1.82 g, 66% yield). ^{1}H-NMR data were in agreement with those reported for this compound.[14]

(*R*)-1-Undecyn-3-ol (8). Alkynyl ketone **4** (3.00 g, 18.02 mmol) was added under a nitrogen atmosphere to neat *R*-Alpine-Borane^R (36.14 mmol, obtained from evaporation of the solvent of 72.3 mL of the 0.5 M commercial solution in THF under a nitrogen atmosphere). The resulting mixture was stirred at room temperature (15 h reaction time). After completion of the reaction, the mixture was cooled to 0 °C and freshly distilled propionaldehyde (2.10 g, 36.14 mmol) was added to destroy the excess reagent (1 h reaction time). Liberated α-pinene was removed *in vacuo* (10^{-3} mbar) at 40 °C, and the residue was dissolved in anhydrous ethyl ether (48 mL). The solution was cooled to 0 °C and ethanolamine (2.21 g, 36.14 mmol) was added to remove 9-BBN. After 15 min, the 9-BBN-ethanolamine adduct was filtered through a sintered glass funnel. The precipitated was washed (2 x 5 mL) with cold ether. The combinated filtrate and washings were dried on anhydrous sodium sulfate, and the ether evaporated at reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 9:1 as eluant). A colourless oil was obtained (2.81 g, 92% yield, 91% e.e. determined by ^{1}H- NMR shift reagent experiment). $[\alpha]_D^{20}$ = + 13.7 (c 0.86, diethyl ether).[15] GC/MS (70 eV) 167(<1), 139(1), 135(1), 121(6), 107(10), 93(26), 83(28), 79(46), 71(39), 70(59), 57(63), 55(100), 43(89), 41(76). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.19-1.34 (m, 10H), 1.38-1.47 (m, 2H), 1.62-1.75 (m, 2H), 1.83 (bs, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 4.34 (td, *J* = 6.6, 2.1 Hz, 1H) ppm.

(*R*)-3-*t*-Butyldimethylsilyloxy-1-undecyne (2). A mixture of alcohol **8** (2.50 g, 14.84 mmol), *t*-butyldimethylchlorosilane (3.36 g, 22.29 mmol) and imidazole (2.53 g, 37.16 mmol) in DMF (2 mL) was stirred at room temperature for 2 h, then diluted with water (20 mL) and extracted with ethyl acetate (3x50 mL). The organic phases were washed with 1 N aqueous hydrochloric acid, then with water and dried over anhydrous sodium sulphate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography (petroleum ether as eluant); a colourless oil was obtained (3.41 g, 81% yield).$[\alpha]_D^{20}$ = +34.9 (c 1, chloroform). GC/MS (70 eV) 225(6), 169(5), 113(71), 83(35), 75(100), 73(26), 69(17), 57(15), 55(18), 43(24), 41(31). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 1.20-1.35 (m, 12H), 1.58-1.70 (m, 2H), 2.36 (d, *J* = 2.0 Hz, 1H), 4.32 (td, *J* = 6.4, 2.0 Hz, 1H) ppm.

Methyl (E)-9-trimethylsilyl-5-oxo-8-nonaen-6-ynoate (5). The methyl glutaryl chloride/$AlCl_3$ complex was prepared by dropwise addition of a solution of the acyl chloride (1.75 g, 10.63 mmol) in CH_2Cl_2 (10 mL)

to a stirred suspension of $AlCl_3$ (2.82 g, 21.15 mmol) in CH_2Cl_2 (20 mL) under a nitrogen atmosphere at 0 °C. The resulting clear solution was then added dropwise to a stirred solution of bis(trimethylsilyl)enyne **9**[10] (1.90 g, 9.67 mmol) in CH_2Cl_2 (20 mL) at 0°C. On completion of the reaction (1h reaction time), an aqueous saturated solution of NH_4Cl (50 mL) was carefully added, and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic phases were washed with water and dried on anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate 10:1.5); 2.02 g (83% yield) of colourless oil were obtained. IR (neat) ν 2184, 1741,1673, 1251, 980, 865, 844 cm^{-1}. GC/MS (70 eV) 237(6), 221(19), 166(20), 151(51), 123(100), 89(37), 75(40), 73(25), 59(50), 55(63). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.90 (q, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 3.58 (s, 3H), 5.96 (d, *J* = 19.4 Hz, 1H), 6.73 (d, *J* = 19.4 Hz, 1H) ppm.

Methyl (5*S*, 8*E*)-9-trimethylsilyl-5-hydroxy-8-nonaen-6-ynoate (10). The alcohol **10** was obtained by reduction of ketone **5** (3.43 g, 13.59 mmol) with neat *S*-Alpine-borane[R] (27.22 mmol, obtained from evaporation of the solvent of 54.4 mL of a 0.5 M solution in THF under a nitrogen atmosphere) following the procedure previously described for reduction of the acetylenic ketone **4** (15 h reaction time). The excess of reagent was destroyed with freshly distilled acetaldehyde (1.20 g, 27.40 mmol); BBN was removed by adding ethanolamine (1.68 g, 27.50 mmol). The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 7:3), affording 3.17 g (91% yield, 83% e.e. determined by HPLC, hexane/isopropanol 95:5, 1 mL/min) of a colourless oil. $[\alpha]_D^{20}$ = – 3.49 (c 15, chloroform). IR (neat) ν 3436, 1741, 978, 867, 842. GC/MS (70 eV) 239 (1), 181(16), 166(15), 165(14), 153(18), 151(17), 125(23), 105(20), 91(28), 89(38), 75(100), 73(63), 59(51). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.60-1.90 (m, 4H), 2.05 (bs, 1H), 2.37 (t, *J* = 7.1 Hz, 2H), 3.66 (s, 3H), 4.45-4.55 (bm, 1H), 5.93 (dd, *J* = 19.3, 1.7 Hz, 1H), 6.43 (dd, *J* = 19.3, 0.5 Hz, 1H) ppm.

Methyl (5*S*, 8*E*)-9-trimethylsilyl-5-*t*-butyldimethylsilyloxy-8-nonaen-6-ynoate (11). A mixture of alcohol **10** (2.91 g, 11.44 mmol), *t*-butyldimethylchlorosilane (2.59 g, 17.18 mmol), and imidazole (1.95 g, 28.64 mmol) in DMF (2 mL) was stirred at room temperature for 2 h, then diluted with water (20 mL) and extracted with ethyl acetate (3x50 mL). The organic phases were washed with 1 N aqueous hydrochloric acid, then with water and dried over anhydrous sodium sulphate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography (petroleum ether/ethyl acetate 92:8); 3.57 g (85 % yield) of colourless oil were obtained. $[\alpha]_D^{20}$ = - 29.9 (c 15, chloroform). IR (neat) ν 1745, 1252, 1096, 979, 868, 842 cm^{-1}. GC/MS (70 eV) 353(2), 337(4), 311(48), 281(21), 187(51), 181(12), 147(33), 145(19), 89(35), 75(39), 73(100), 59(27). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.10 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.65-1.85 (m, 4H), 2.34 (t, *J* = 7.3 Hz, 2H), 3.66 (s, 3H), 4.48 (td, *J* = 6.03, 1.6 Hz, 1H), 5.93 (dd, *J* = 19.3, 1.6 Hz, 1H), 6.36 (d, *J* = 19.3 Hz, 1H) ppm.

Methyl (5*S*, 6*Z*, 8*E*)-9-trimethylsilyl-5-*t*-butyldimethylsilyloxy-6,8-nonadienoate (12). The ester **11** (3.37 g, 9.14 mmol), $Pd/BaSO_4$ (Pd 5 %, 0.84 g), quinoline (0.34 mL) were treated with hydrogen (1 atm) at room temperature until gas absorption stopped (about 380 mL of gas were absorbed). The solvent was evaporated at reduced pressure and the catalyst removed by percolation on florisil column (petroleum ether/ethyl acetate 98:2 as eluent). A colourless oil (3.37 g, 100% yield) was obtained. $[\alpha]_D^{20}$ = + 20.7 (c 15, chloroform). IR (neat) ν 1743, 1250, 1088, 1005, 867, 841, 777 cm^{-1}. GC/MS (70 eV) 370(<1), 313(15), 147(22), 89(22), 75(34), 73(100), 59(22), 55(15). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.07 (s, 9H), 0.85 (s, 9H), 1.35 -1.74 (m, 4H), 2.30 (t, *J* = 7.4 Hz, 2H), 3.64 (s, 3H), 4.55-4.62 (m, 1H), 5.34 (t, *J* = 10.9 Hz, 1H), 5.86 (d, *J* = 18.2 Hz, 1H), 5.93 (t, *J* = 10.9 Hz, 1H), 6.72 (dd, *J* = 18.2, 10.9 Hz, 1H) ppm.

Methyl (5*S*, 6*Z*, 8*E*)-9-bromo-5-*t*-butyldimethylsilyloxy-6,8-nonadienoate (3). *N*-bromosuccinimide (1.73 g, 9.71 mmol) was added at -30 °C to a solution of **12** (3.61 g, 9.74 mmol) in 100 mL of DMF, then the temperature was allowed to rise to 0 °C. The reaction was monitored by TLC (petroleum ether/ethyl acetate 97:3). After 6 h the reaction was completed, and water (300 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 100 mL); the organic phases were washed with water (3 x 100 mL) and dried over sodium sulphate. The residue obtained by evaporation of the solvent at reduced pressure was purified by flash chromatography; a colourless oil was obtained (2.21 g, 59% yield). $[\alpha]_D^{20}$ = + 23.9 (c 15, chloroform). IR (neat) ν 1743, 1257, 1091, 933, 841, 812, 780 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.50-1.75 (m, 4H), 2.30 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 3H), 4.42-4.49 (m, 1H), 5.41 (dd, *J* = 11.3, 8.5 Hz, 1H), 5.84 (t, *J* = 11.3 Hz, 1H), 6.31 (d, *J* = 13.3 Hz, 1H), 6.94 (dd, *J* = 13.3, 11.3 Hz, 1H) ppm.

Methyl (5*S*, 12*R*, 6*Z*, 8*E*, 10*E*)-5,12-bis(*t*-butyldimethylsilyloxy)-6,8,10-eicosatrienoate (13). The propargylic alcohol **2** (0.20 g, 0.71 mmol) was treated with cathecolborane (0.09 g, 0.71 mmol) under a nitrogen atmosphere at room temperature. After 12 h benzene (10 mL) was added to the reaction mixture, and the resulting solution was added dropwise to a benzene (20 mL) suspension of bromoderivative **3** (0.24 g, 0.64 mmol) and tetrakistriphenylphosphine palladium (0) (0.19 g, 0.17 mmol), previously stirred for 0.5 h. Then an aqueous 2 M NaOH solution (0.65 mL, 1.3 mmol) was added, and the resulting heterogeneous mixture was vigorously stirred for 1 h at room temperature. Water (20 mL) was added, the organic phase separated and the water phase extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with aqueous HCl (1.2 M, 20 mL), then with water (20 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the crude product was purified by flash chromatography (petroleum ether/ethyl acetate 96:4). A colourless thick oil was obtained (0.21 g, 57% yield). $[\alpha]_D^{20}$ = + 12.1 (c 1, chloroform). IR (neat) ν 1728, 1239, 1070, 990, 822, 761 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.01(s, 3H), 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.83-0.90 (m, 21H), 1.17-1.73 (m, 18H), 2.30 (t, 7.4 Hz, 2H), 3.64 (s, 3H), 4.08-4.18

(m, 1H), 4.50-4.57 (m, 1H), 5.34 (dd, J = 11.2, 8.7 Hz, 1H), 5.67 (dd, J = 14.3, 6.4 Hz, 1H), 5.93 (t, J = 11.2 Hz, 1H), 6.08-6.20 (m, 2H), 6.29-6.39 (m, 1H) ppm.

LTB_3 methyl ester (1). The deprotection reaction of **13** was performed following a reported procedure.[16] Neutral Al_2O_3 (100-125 mesh, 6.0 g) was added under a nitrogen atmosphere to a solution of **13** (0.052 g, 0.090 mmol) in hexane (8 mL). The resulting slurry was stirred at room temperature, and the progress of the reaction was monitored by TLC until disappearance of the starting silyl ether (12 h reaction time). After reaction completion, the mixture was filtered through a sintered glass funnel (No. 4) and the alumina washed with ethyl acetate (50 mL). The combined organic phases were concentrated at reduced pressure. After flash chromatography of the crude product, 0.013 g (41% yield) of LTB_3 methyl ester were obtained. $[\alpha]_D^{20}$ = + 6.0 (c 1, chloroform). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 6.3 Hz, 3H), 1.10-1.16 (m, 20H), 2.30 (t, J = 7.2 Hz, 2H), 3.64 (s, 3H), 4.11-4.18 (m, 1H), 4.50-4.56 (m, 1H), 5.36 (t, J = 11.5 Hz, 1H), 5.72 (dd, J = 14.9, 6.8 Hz, 1H), 5.94 (t, J = 11.5 Hz, 1H), 6.18 (dd, J = 14.5, 10.7 Hz, 1H), 6.26 (dd, J = 10.7, 14.9 Hz, 1H), 6.39 (dd, J = 14.5, 11.5 Hz, 1H) ppm. A second minor product was isolated (0.002 g, 6% yield), very likely corresponding to the other diastereoisomer.[13]

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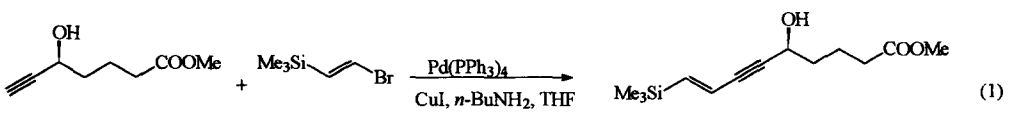
REFERENCES AND NOTES

1. Maycock, A.L.; Sheng-shung, P.; Evans, J.F.; Miller, D.K. Biochemistry of the Lipoxygenase Pathways. In *Leukotrienes and Lipoxygenase*; Rockack, J. Ed.; Elsevier: New York, 1989; pp 143-208. Green, R.H.; Lambeth, P.F. *Tetrahedron*, **1983**, *39*, 1687-1721.
2. Jones, T.R.; Letts, G.; Chi-Chung, C.; Davies, P. Pharmacology and Pathophysiology of Leukotrienes. In *Leukotrienes and Lipoxygenase*; Rockack, J. Ed.; Elsevier: New York, 1989; pp 309-403.
3. Evans, J.; Zamboni, R.; Nathaniel, D.; Leveille, C.; Ford-Hutchinson, A.W. *Prostaglandins*, **1985**, *30*, 981-988. Lee, T.H.; Sethi, T.; Crea, A.E.G.; Peters, W.; Arm, J.P.; Horton, C.E.; Walport, M.J.; Spur, B.W. *Clin. Sci.*, **1988**, *74*, 467-475.
4. On the LTB_4 synthesis see: a) Cotteril, I.C.; Dorman, G.; Faber, K.; Jahouari, R.; Roberts, S.M.; Scheinmann, F.; Spreitz, J.; Sutherland, A.G.; Winders, J.A.; Wakefield, B.J. *J. Chem. Soc., Chem. Commun.* **1990**, 1661-1663. b) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324-5335. c) Avignon-Tropis, M.; Treilhou, M.; Pougny, J.R.; Fréchard-Ortuno, I.; Linstrumelle, G. *Tetrahedron* **1991**, *47*, 7279-7286. d) Borer, B.C.; Taylor R.J.K. *Synlett* **1992**, 117-118. e) Avignon-Tropis,

M.; Berjeaud, J.M.; Pougny, J.R.; Fréchard-Ortuno, I.; Guillerm, D.; Linstrumelle, G. *J. Org. Chem.* **1992**, *57*, 651-654. f) Treilhou, M.; Fauve, A.; Pougny, J.R.; Promé, J.C.; Veschambre, H. *J. Org. Chem.* **1992**, *57*, 3203-3208. g) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1992**, *48*, 1943-1952. h) Kerdesky, F.A.; Schmidt, S.P.; Brooks, D.W. *J. Org. Chem.* **1993**, *58*, 3516-3520. i) Peng, Z-H.; Li Y-L.; Wu, W-L.; Liu, C-X.; Wu, Y-L. *J. Chem. Soc., Perkin Trans 1*, **1996**, 1057-1066.

5. For the synthesis of LTB_3 and some other derivatives see: a) Spur, B.; Crea. A.; Peters, W. *Arch. Pharm.* **1985**, *318*, 225-228. b) Nakamura, T.; Nakamiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635-2645. c) Phythian, S.J.; Taylor, R.J.K.; Bantick, J.R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 194-195. d) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.H. *J. Org. Chem.* **1990**, *55*, 6203-6214.
6. a) Babudri, F.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Chem. Soc., Chem. Commun.* **1991**, 237-239. b) Babudri, F.; Fiandanese, V.; Naso, F. *J. Org. Chem.* **1991**, *56*, 6245-6248. c) Babudri, F.; Fiandanese, V.; Naso, F.; Punzi, A. *Synlett* **1992**, 221-223. d) Fiandanese, V.; Punzi, A. *Synth. Commun.* **1993**, *23*, 173-182. e) Babudri, F.; Fiandanese, V.; Naso, F.; Punzi, A. *Tetrahedron Lett.* **1994**, *35*, 2067-2070. f) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Synlett* **1995**, 817-818. g) Babudri, F.; Cicciomessere, A.R.; Farinola, G.M.; Fiandanese, V.; Marchese, G.; Musio, R.; Naso, F.; Sciacovelli, O. *J. Org. Chem.* **1997**, *62*, 3291-3298.
7. The ketone **4** can be also obtained in a single step by acylation reaction of simple trimethylsilylacetylene. However the yield of **4** was considerably poorer than the overall yield resulting from the two steps route described in the text.
8. a) Brown, H.C.; Pai, G.G. *J. Org. Chem.* **1985**, *50*, 1384-1394. b) Midland, M.M.; Tramontano, A.; Kazubski, A.; Graham, R.S.; Tsai, D.J.S.; Cardin, D. *Tetrahedron* **1984**, *40*, 1371-1380.
9. The absolute configuration of **10** was expected to be *S* on the basis of the stereochemical course followed by reduction of similar substrates. Nevertheless such a configuration was unambiguously established by preparing the same compound from the *S* propargylic alcohol **14**[48] according to a known reaction (eq. 1). See: Dieck, H.A.; Heck R.F. *J. Organomet. Chem.* **1975**, *93*, 259-263. Cassar, L. *J. Organomet. Chem.*. **1975**, *93*, 253-257. Sonogashira, K.; Tohda Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.



(1)

14 **15** **10** $[\alpha]_{20}^{D}$ = -3,66 (c 15, chloroform)

10. Fiandanese, V.; Marchese, G.; Punzi, A.; Ruggieri, G. *Tetrahedron Lett.* **1996**, *37*, 8455-8458.
11. Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100-1106.
12. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
13. The ^{1}HNMR spectrum was identical in the vinyl region to the spectrum of compound **1**.

14.Katritzky, A.R.; Lang H. *J. Org. Chem.* **1995**, *60*, 7612-7618.

15.Mori, K.; Nukada, T.; Ebata, T. *Tetrahedron* **1981**, *37*, 1343-1347. Johnson, W.S.; Elliott, R.; Elliott, J.D. *J. Am. Chem. Soc.* **1983**, *105*, 2904-2905.

16.Feixas, J.; Capdevila, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 8539-8550.